

DELIBERATE ARTERIAL HYPOTENSION

Studies on Clinical, Hemodynamic, and
Biochemical Changes during Hypotension
Induced by Trimethaphan, Sodium Nitroprusside
and Glycerol Trinitrate

by

Afzal K. Vazeery



Lund 1983

Malmö 1983

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From the Departments of Anesthesiology, Orthopedic Surgery, Plastic Surgery, and Clinical Biochemistry, Central Hospital of Rogaland, Stavanger, Norway; and the Departments of Anesthesiology and Plastic surgery, Malmö General Hospital, University of Lund, Malmö, Sweden.

Malmö 1983



To Shokouh (my wife) and Yari (our son) who endured the numerous challenges during my six-year long undertaking, with resolute perseverance.

Notwithstanding many sources of doubt, man can generally and readily distinguish between the higher and the lower moral rules. The higher are founded on the social instincts, and relate to the welfare of others. They are supported by the approbation of our fellow-men and by reason.

(The descent of man, Charles Darwin, 1871)

This thesis is based on the following papers:

- I CONTROLLED HYPOTENSION IN HIP-JOINT SURGERY: AN ASSESSMENT OF SURGICAL HAEMORRHAGE DURING SODIUM NITROPRUSSIDE INFUSION.
A. K. Vazeery and O. Lunde.
Acta Orthop. Scand. 50, 344, 1979.
- II DELIBERATE ARTERIAL HYPOTENSION IN PLASTIC SURGERY FOR THE REDUCTION OF HYPERTROPHIC BREAST: A CRITICAL APPRAISAL OF SURGICAL ISCHAEMIA AND HAEMODYNAMIC CHANGES DURING SODIUM NITROPRUSSIDE INFUSION.
A. K. Vazeery, K. Aspelund and I. Ahlgren.
Scand. J. Plast. Reconstr. Surg. 14, 133, 1980.
- III HEMODYNAMIC CHANGES DURING SODIUM NITROPRUSSIDE AND TRIMETHAPHAN INFUSIONS WITH CONCURRENT MODERATELY HIGH DOSAGE FENTANYL ANESTHESIA: AN INVASIVE AND NONINVASIVE STUDY DURING HIP ARTHROPLASTY.
A. K. Vazeery, P. Lunde and A. Högberg
Submitted for publication.
- IV SODIUM NITROPRUSSIDE AS A HYPOTENSIVE AGENT IN SURGERY: DETERMINATION OF THE MINIMUM DOSAGE REQUIREMENT WITH MODERATELY HIGH DOSES OF FENTANYL.
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- V. CHANGES IN CARDIAC OUTPUT AND SYSTEMIC BLOOD PRESSURE AFTER INSERTION OF ACRYLIC CEMENT DURING TRIMETHAPHAN, NITROPRUSSIDE AND GLYCEROL TRINITRATE (NITROGLYCERIN)-INDUCED HYPOTENSION: A COMPARISON WITH CHANGES DURING NORMOTENSION.
A. K. Vazeery, S. Skeie and O. Anda
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INTRODUCTION

The profuse hemorrhage encountered often in major surgical interventions has led physicians to master innovative techniques which would curtail the undesirable blood loss. Massive bleeding would, for example, hinder the removal of extremely vascular lesions, or an abrupt and plaguing hemorrhage would sabotage the results of a painful and time-consuming surgical undertaking. From the vantage point of today's era of meticulous continuous monitoring, it is hard to believe that anesthesiologists manipulated daring hypotensive techniques relying only upon the auscultative methods of measuring the systemic blood pressure and a manual recording of the radial pulse.

Medical literature records the untoward mishaps faced by the early pioneers of induced hypotension. This considerable documentation led to consistent criticism of the technique, which was in its embryonic form and probably used unrestrictively, in the fifties. Anesthesiologists engaged in the practice of producing deliberate hypotension under challenging surgical manoeuvres encountered periodic disappointments. They reacted, however, as forthrightly as those involved with the other branches of medicine and persevered to minimize the pitfalls in the existing methods. They believed in deliberate ischemia in arduous conditions, through the bitter lessons learned and while accepting relatively more selective indications.

Looking back into the short history of diminished bleeding during surgery, it is obvious that in its early days it was employed not only to facilitate surgical plans, but that a compelling motivator was the desire to solve the dilemma of the deleterious effects of massive blood transfusions which,

although often not fatal, were a constant worry to those devoted to the treatment of massive disorders. Many of the potential problems supervening during transfusions, or encountered during intricate operative procedures, have been eliminated by deliberately lowering systemic blood pressure to levels which ensure an ischemia of the surgical wound.

The manipulation of hypotension as a facilitatory adjunct to neurosurgery was first conceived by Cushing in 1917 (1). He noted that hemorrhagic hypotension was followed by compensatory vasoconstriction which led to a dry operating wound. Pitkin in 1928 described the beneficial effects of spinal anesthesia in patients who were a bad risk for ether inhalation (2). The marvels of securing "nice dry wounds" were appraised by him when he called the method a controllable spinal anesthesia.

Sodium nitroprusside was first described by Hermann in 1886 (3). Its actions as a potent vasodilator which included the property of lowering blood pressure in experimental animals, were elaborately investigated by Johnson in 1924 (4). He demonstrated that the intravenous use of sodium nitroprusside, in definitely minimum effective doses, lowered blood pressure in rabbits and that it was 1000 times as efficient as sodium nitroprusside.

The technique of blood-letting through arteriotomy and thereby securing hypotension was first performed experimentally by Kohlstaedt and Page in 1943 (5). The restoration of blood pressure was proposed by the re-transfusion of blood intra-arterially or via the intravenous route. When arteriotomy was employed clinically by Gardner in 1946 (6), and Bilsland in 1951 (7), it was realised that the human patients were being deliberately subjected to a situation which, in many aspects, simulated shock. Sharp criticism and abandonment followed when Gillies in 1952 correctly defined the practice as a trespass in anesthesia (8).

Effective ischemia of the operative field was achieved clinically by Griffiths and Gillies in 1948 who described the beneficial effects of thoraco-lumbar sympathetic blockade through high spinal anesthesia(9).

This was a period when many surgeons and anesthesiologists created a lot of uproar. They condemned the clinicians for applying methods where knowledge was lacking as to the concurrent changes which might take place in such essential organs as the brain, heart, liver and kidney. One of the most convincing objections was that the "dry field" was being produced to please the surgeon no matter how detrimental it might prove to be to the patient. It was during this period of dilemma, and in an atmosphere of justifiable condemnation, that Enderby in 1950 pioneered the first application of a ganglion blocking agent: pentamethonium iodide, to reduce the blood pressure during surgery by intention (10). He called it controlled circulation. Many others followed suit, using the drug while critically appraising the hypotensive agent and its effects on their patients. Pentolinium tartarate, thought to have certain advantages over the other, was introduced in 1954 (11). Arfonad (trimethaphan) was added to the armamentarium of an anesthesiologist when its short-acting sympatholytic properties were evaluated by Randall and his colleagues in 1949 (12) and later by others (13,14).

Controlled hypotension, which had previously been monopolized by a handful of enthusiasts, was now adopted by a greater number of physicians due to a minute-to-minute regulation of blood pressure being made possible through a continuous administration of the evanescent action of the hypotensive drug. By using the advanced monitoring techniques of recent years the induction of surgical ischemia is no longer cumbersome for its practioners. Current

availability of the potent vasodilators, such as sodium nitroprusside and nitroglycerin which were introduced into hypotensive anesthesia by Moraca in 1962 (15) and Fahmy in 1978 (16), respectively, have far wider implications than the aforementioned ganglion-blocking drugs.

The research conducted in the field of deliberate ischemia during the last two decades has been outstanding. Surgery which was very irksome for many pathological conditions is becoming routine using controlled hypotension. Halothane, which has been used by many as a sole hypotensive agent, is employed now as an adjuvant.

AIMS OF THE INVESTIGATIONS

- To develop a method by which elderly patients may benefit maximally during controlled arterial hypotension using a combination of potent vasodilators and balanced anesthesia (without inhalation anesthesia).
- To investigate the changes in cardiovascular dynamics under moderately high-dosage fentanyl anesthesia with minimal possible amounts of vasodilators or alternative hypotensive drugs (ganglion blockers).
- To determine the minimal dosage of the vasodilator of choice required during induced hypotension, with intensive monitoring in the presence of deep fentanyl analgesia and in a variety of surgical procedures.
- To study a large number of patients with particular regard to the clinical and circulatory changes during surgery under deliberate ischemia via non-invasive impedance plethysmography.
- To analyse the benefits, as well as the pitfalls, of controlled ischemia in surgery and to draw a comparison with normotensive anesthesia.
- To assess the practicality of developed hypotensive anesthetic technique at a modern medical center.

MATERIAL

Clinical investigations consisted of 203 patients undergoing total hip replacement, fixation of femur and plastic reconstructive surgery for various indications such as hypertrophy of breast or deflected nasal septum. Through a customary preoperative assessment any patient with cerebral, cardiac, renal or hepatic pathology was excluded from this investigation.

In paper I, 50 patients were randomized into two groups. Preoperatively all patients were normovolemic and comparable in age, weight, hemoglobin and hematocrit. In 25 normotensive patients (mean age 70, range 57-86 years) the operative blood loss was replaced by bank blood whereas the 25 hypotensive patients (mean age 74, range 55-80 years) needed no transfusion.

In paper II, 40 women undergoing plastic surgery for bilateral hypertrophy of the breast were studied. Fourteen patients (mean age 38, range 22-52 years) were operated on under arfonad-induced hypotension. In 13 patients (mean age 35, range 19-61 years) surgical ischemia was produced by nitroprusside infusion. Intraoperative circulatory changes were investigated only in this group. Fourteen patients (mean age 40, range 20-57 years) underwent surgery under deep neuroleptanesthesia and normotension, and served as a control group.

In paper III, intraoperative cardiovascular hemodynamics was studied in 29 patients who were all operated on for cox-arthritis with Charnley's prosthesis. In 15 patients (mean age 68, range 53-76 years) operations were performed during trimethaphan (arfonad)-induced hypotension, while 14 patients (mean age 69, range 57-73 years) underwent arthroplasty during nitroprusside infusion. All patients were operated on under deep fentanyl anesthesia. The preoperative, but post-induction, values of various hemodynamic parameters served as their own controls in both groups.

In paper IV, 47 patients were studied. They were randomized into two groups. Twenty-four patients (mean age 45, range 20-76 years) underwent surgery during nitroprusside-induced hypotension and moderately high-dosage fentanyl anesthesia, while 23 patients (mean age 47, range 23-71 years) were operated on under balanced (low-dosage fentanyl) anesthesia and nitroprusside. They served as the control group.

In paper V, the clinical investigation was composed of 37 patients who were operated on for hip osteoarthrosis. Nine patients (mean age 69, range 55-72 years) received trimethaphan. In 8 patients (mean age 70, range 57-75 years) arthroplasty was done during nitroprusside-induced hypotension; 9 patients (mean age 65, range 59-70 years) underwent surgery under nitroglycerin hypotension. Changes in cardiac output, heart rate and the mean arterial pressure were monitored intraoperatively before and after the insertion of acrylic cement in acetabulum or femur. Studies of similar changes were conducted in 11 patients (mean age 69, range 57-79 years) who were operated on under normotension. They served as control group.

METHODS

The basis of clinical investigation was the monitoring of the effects of the currently available hypotensive agents trimethaphan, nitroprusside and nitroglycerin in combination with a potent narcotic: fentanyl, a derivative of meperidine. A thorough study was done of any potential consequences of this combination on biochemistry and hemodynamics within the allowed therapeutic doses. Droperidol was included in paper II, while halothane was used as an adjunct in 3 investigations (paper I, II and IV). The various invasive and non-invasive procedures performed on the patients were as follows:-

Invasive measurements

Generally, in all the investigations, the mean arterial pressure was estimated continuously after the insertion of a plastic infusion cannula (venflon 1.2 mm, AB Viggio, Sweden) percutaneously in a radial artery. It was recorded by a disposable Pressurveil transfer unit with a membrane depressor tube connected directly to a pressure gauge (Concept Inc. USA).

For the measurement of central venous pressure, a plastic infusion cannula (Drum-cartridge catheter 1.8 mm, Venisystems, USA), was inserted into the antebrachial vein and connected via the aforementioned Pressurveil unit to a low pressure gauge (papers II and III).

Infusions of the three hypotensive agents employed in this study were regulated through an infusion pump (IVAC 531, USA), and given separately via an additional venflon cannula (1.2 mm).

Mean arterial pressure was estimated constantly by the arterial pressure gauge (Taylor, Mod. II sphygmomanometer, Concept Inc.), in all the investigations excepting one in paper II, where a minute-to-minute measurement, during arfonad infusion was rendered by the Instrument electric sphygmomanometer (Cardi 8 mini, Japan).

Central venous pressure was estimated by a low pressure gauge (Taylor, Concept Inc.), in paper II and III.

Rectal temperatures were recorded continuously during all orthopedic operations being conducted in a cold environment (Charnley's green-house) by a thermocouple (Electrolaboratories, Denmark) to avoid hypothermia.

Arterial gas tensions and pH were measured with conventional electrodes for papers I, III, IV and V by Radiometer (ABL 2, Denmark). The blood samples were collected in disposable plastic syringes, analyzed at 37⁰C and corrected to the actual registered rectal temperature.

Hematocrit and Hemoglobin values were taken pre- and post-operatively in paper I and IV. In paper II intraoperative determinations of hematocrit were made additionally during nitroprusside infusion. In papers III and V pre-, intra- and postoperative hematocrit values were determined.

Blood loss was estimated by weighing the wet swabs and towels intraoperatively (papers I, II and III). Postoperative blood loss was measured through plastic suction drainage bottles.

Assay of sodium thiocyanate in plasma

The plasma thiocyanate was determined by the spectrophotometric method of Aldridge (17). Potassium thiocyanate (KCN) solutions of known concentration were used as standards. Plasma thiocyanate was determined on duplicate 1-ml aliquots of the supernatant obtained by centrifuging a mixture of 1 ml of plasma and 9 ml of 10% trichloroacetic acid thereby deproteinizing the plasma. Base-line samples of arterial blood were collected immediately before the SNP infusion was started. Blood was withdrawn into a pre-cooled heparinized syringe, sealed and placed in a mixture of ice and water. Subsequent samples of arterial blood were obtained 15 minutes, 45 minutes, 3 hours and 24 hours after the commencement of SNP infusion.

Statistical methods

Statistical and mathematical calculations were made on a desk calculator (Texas Instruments, model TI Programmable 57) using a specially made program for each problem. Calculations were made of the mean (M), standard deviation (SD) and standard error of the mean (SEM). Comparisons were carried out with the use of Student's t-test for paired observations or for means of two samples.

Degrees of significance were marked as follows:-

* $0.05 > P > 0.01$; ** $0.01 > P > 0.001$; *** $P < 0.001$

Measurement of hemodynamic changes

Since a greater number of patients were included in the investigation, the hemodynamic changes were monitored by the convenient, non-invasive method of electrical impedance plethysmography. The purpose of the measurements was explained to all the patients and they consented to participate in the study.

Stroke volume and cardiac output

A four electrode impedance plethysmographic system was used. The electrodes consisted of a self-adhesive disposable Mylar strip carrying an aluminium band. Two band electrodes [1 and 2] were placed around the patient's neck, a third band around the thorax at the level of xiphisternal joint [3], and the fourth band around the abdomen [4]. A constant sinusoidal alternate current of 4 mA r.m.s. at 100 kHz was applied between the two outer current electrodes [1 and 4]. The resultant voltage (impedance) changes appearing across thorax with the cardiac cycle were monitored from the inner two electrodes [2 and 3]. The cardiac activity was amplified by the Minnesota impedance cardiograph (Model 304 A, Instrumentation for Medicine, Inc. USA). Fig. 1 & 2 illustrate the principle of the electrical impedance technique for measuring the cardiac function. The outer two electrodes were placed at least three centimeters from the inner electrodes. Both the outer current electrodes and the inner potential electrodes were internally connected to isolation transformers to limit the maximum possible earth leakage to the patient, to within 40 μ A. The average impedance between electrodes [2 and 3] (Z_0) appearing across the thorax at 100 kHz in a healthy adult is 25.0 ohms. At rest, this value decreases by 0.1-0.15 ohms during the cardiac cycle (Z). The 3 signals yielded by the impedance cardiograph namely the peak negative value of the first time derivative of the cardiac cycle (dz/dt), phonocardiogram and ECG,

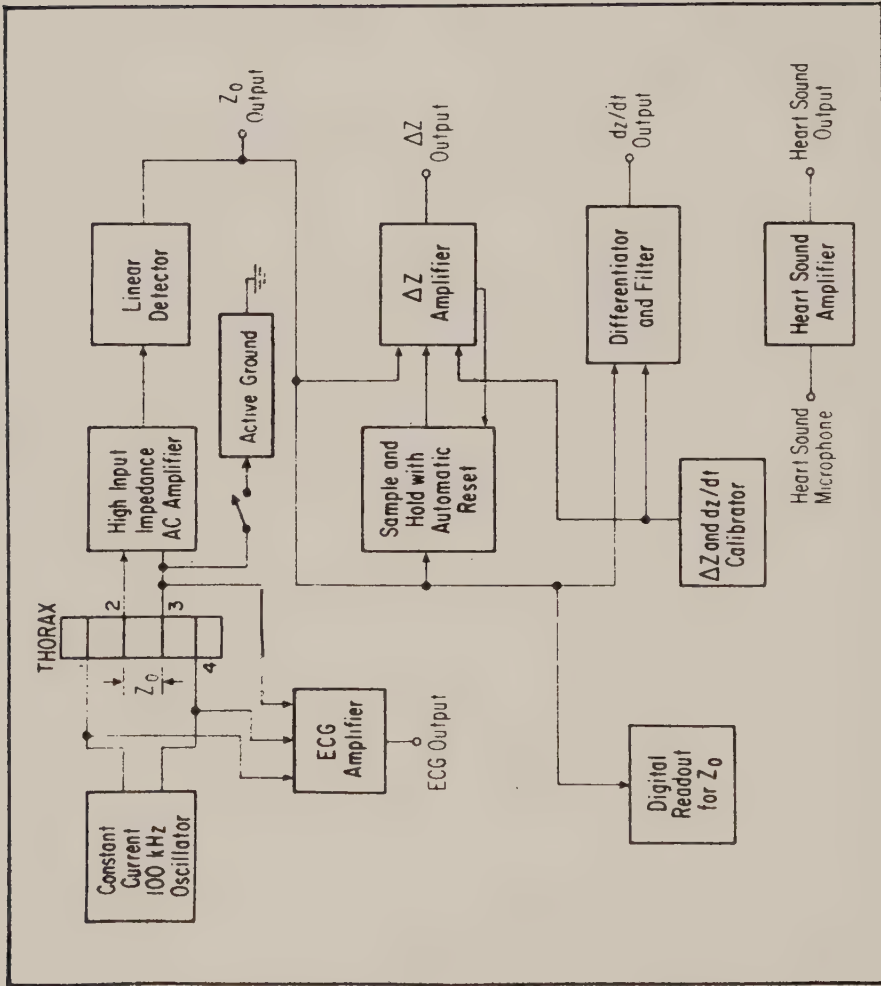


Fig. 1. A block diagram of the main circuit elements of the IFM Impedance Cardiograph (by the courtesy of Instrumentation for Medicine Inc. USA).

were displayed on a four-channel heated stylus graphic recorder using a paper speed of 50 mm. sec^{-1} for stroke volume measurements.

Stroke volume was calculated from the following equation:

$$\Delta V = \rho \cdot \frac{L^2}{Z_0^2} \cdot T \cdot (dZ/dt)_{\min} \quad [\text{Equation I}]$$

where

ΔV = the ventricular stroke volume (ml)

ρ = the electrical resistivity or specific resistance of blood (ohm-cm) at 100 kHz (correlated to the hematocrit)

L = the mean distance between the two inner electrodes

Z_0 = the basic impedance between the two inner electrodes (ohms)

T = the ventricular ejection time in seconds obtained from the dZ/dt wave form

$dZ/dt_{\min}$ = the minimum value of dZ/dt occurring during the cardiac cycle (ohms.sec)

The average values of ρ were suggested by Kubicek and co-workers to be 150 ohms-cm with a normal hematocrit (HCT), (18,19,20). In clinical practice a wide variation of HCT values is encountered. Therefore, it was later recommended to calibrate the value of ρ for each determination of stroke volume in accordance with blood hematocrit, thereby improving accuracy (21). Hill and Thompson found that with a HCT of 20 per cent, the blood resistivity was reduced to 75 ohms-cm which is only one half of the standard value, initially suggested (22).

We thought it mandatory to estimate the hematocrit values before calculating stroke volume. A standard nomogram was consulted to obtain the corrected values of the specific resistivity of blood at a known HCT level. For detecting the heart sounds a crystal microphone (Hewlett Packard) was used. A calibration signal from the impedance cardiograph corresponding to $dZ/dt = 1 \text{ ohm. sec}^{-1}$ was recorded before all the tracings from the patient. For each beat the peak value of the dZ/dt at systole was noted, as was the ejection time from the

moment the dZ/dt tracing crossed the $dZ/dt = 0$ line at the commencement of systole until the onset of the second heart sound. The phonocardiograms were recorded at the fourth left intercostal space. Independent measurements of the intervals between the electrocardiographic R wave and the points on the first derivative thoracic impedance cardiogram were carried out. The intervals were measured with a millimeter ruler. Beats for measurements were selected on the basis of having recognized phonocardiographic, and first derivative thoracic impedance cardiographic, events. The intervals were measured at an average of four heart beats per calculation and the average of the impedance and the phonocardiographic intervals were compared.

Having calculated the stroke volume from equation I, the mean cardiac output was then obtained by multiplying ΔV , by the instantaneous pulse rate averaged over four beats. In paper II, an average of four tracings of impedance cardiogram were made at least after six calibrations of the cardiograph, before, during and after the application of nitroprusside. In paper III, similar tracings of cardiogram were obtained before, during and after the administration of trimethaphan or nitroprusside.

In paper V, four tracings of impedance cardiogram were carried out at six short intervals after a new calibration before, and immediately after the insertion of acrylic cement into the acetabulum or femur, during controlled hypotension or normotension.

PERIPHERAL BLOOD FLOW

For the measurement of the blood flow in limbs (calf in paper III and forearm in paper IV) the following equation was applied:

$$\Delta V = \rho \cdot \frac{L^2}{Z^2} \cdot \Delta Z \quad \text{[Equation II]}$$

where

ΔV = the volume of blood per beat (ml)

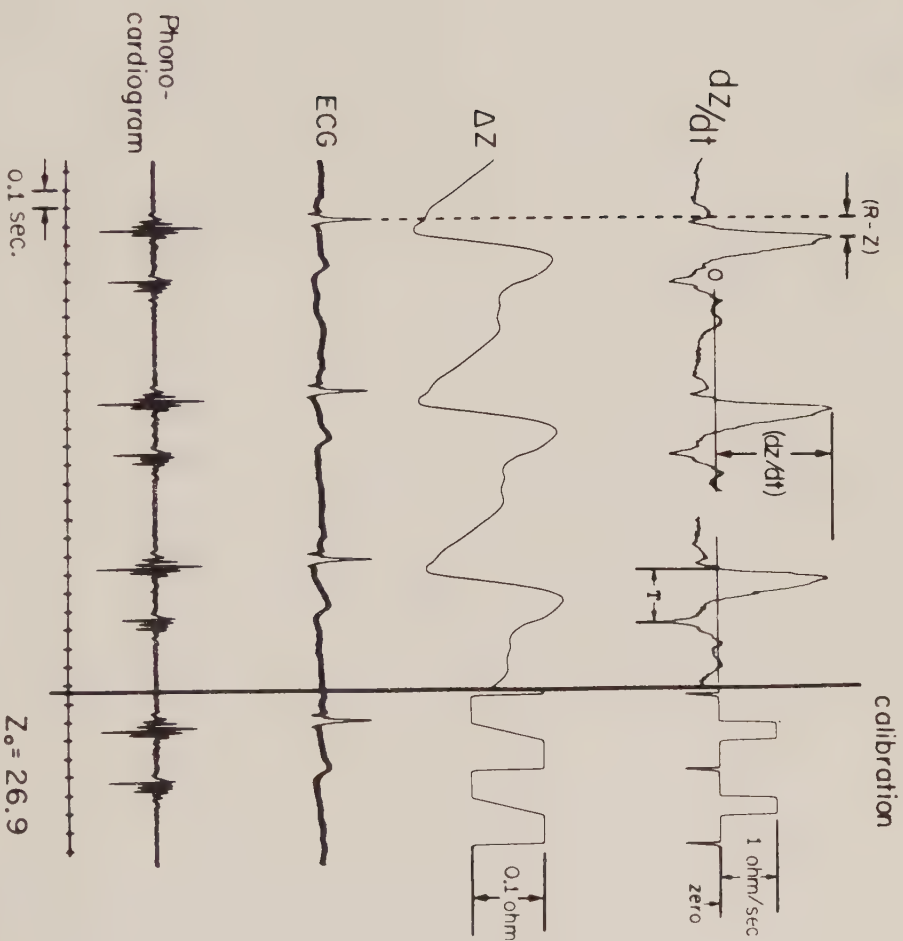


Fig. 2. Typical tracings obtained on a normal subject. Recorder or cardioscope calibration is obtained from the IFM Impedance Cardiograph with the function switch in the "calibration" position, thus providing a ready signal for calculation of stroke volume (by the courtesy of Instrumentation for Medicine Inc. USA).

ρ = the specific resistance of blood

L = the distance between the inner two electrodes

Z_0 = the standing impedance between the two inner electrodes (ohms)

ΔZ = the change of impedance in the peripheral muscle at each cardiac cycle

By multiplying the product of equation II by pulse rate derived from the tracing of the electrocardiogram, the blood flow in the limb per minute was obtained. Before the impedance tracings were carried out, two Mylar aluminium band electrodes [2 and 3] were placed around the calf, or the forearm, muscles. The two outer current electrodes [1 and 4] were placed at least three centimeter from the inner bands.

The stroke volume index and the cardiac index were derived from the nomogram of Barash et al (23), where

$$CI = \frac{CO}{BSA} = L. \min^{-1}. m^2$$

$$SVI = \frac{CI}{P} = ml. \text{ beat}^{-1}. m^2$$

$$BSA = Ht (cm)^{0.725} \cdot Wt (kg)^{0.425} \cdot 71.84 \cdot 10^{-4}$$

(P = pressure, BSA = body surface area, Ht = height, Wt = weight,

CI = cardiac index, SVI = stroke volume index).

Evaluation of bio-electric impedance plethysmography

The electrical impedance of an organ is dependent on the individual resistances and proportions of the components of that organ. Air and fat have comparatively high resistance, whereas the ionized fluids are less resistant (24). It has been established that the impedance offered to the passage of high frequency electric current by the body segments or limbs undergoes rhythmic changes synchronous with myocardial activity.

Impedance plethysmographic measurements have previously been proposed as a sensitive, noninvasive estimation of fluid shifts in thorax and peripheral tissues. Kubicek and his colleagues (18) compared the general cardiac output values calculated by the impedance method and found them larger than the simultaneous values obtained by the dye dilution technique. In comparative clinical investigations entailing cardiac output estimation by transthoracic impedance and dye dilution methods, a correlation of 0.937 (25) and 0.97 (26) was demonstrated in healthy normovolemic individuals. The technique has proved most convenient for the monitoring of relative changes in cardiac output and limb blood flow during anesthesia (27, 28). Its profitable application has been demonstrated in the assessment of changes in thoracic fluid volume (29, 30, 31, 32, 33) or, in the determination of cardiac performance in a number of clinical situations (34, 35, 36, 37).

Gollan and Namon (38) in their experiments on animals have shown that the change of electrical conductivity in moving blood is most likely the property of living red cells, since hemolyzed blood does not possess such properties. The resistance of blood flowing at a constant rate increases with a rise in hematocrit, and it disappears when the blood is hemolyzed.

The basis of extracting the stroke volume and cardiac contractility

indices from thoracic impedance changes is derived from the flowmeter studies on animals, when a linear relationship was obtained by peak dZ/dt and peak ejection rate (21). In the absence of cardiac dysfunction the impedance method yields accuracies nearly equal to the dye dilution or Fick methods (27,39,40,41,42). Although less precise in absolute terms than invasive techniques, the results are reproducible. In order to improve accuracy the calibration of the blood resistivity corresponding to the hematocrit value, is thought to be essential for each calculation of stroke volume. The changes in magnitude are thereby regarded to be comparable with those attained by the dye dilution methods (42).

Anesthetic technique

In paper I, a balanced anesthesia was provided with fentanyl and a mixture of 50-50 per cent oxygen and nitrous oxide gas. Induction was made with brietal sodium 70-100 mg and d-tubocurarine(dTc) 30 mg while further analgesia and muscle relaxation was maintained with supplementary doses of fentanyl and dTc. All patients were moderately hyperventilated. Twenty-five patients received nitroprusside infusion, while another group of 25 patients were operated on under normotension without nitroprusside. A standard premedication of atropine 0.5 mg, pethidine 50-100 mg and promethazine 25-50 mg was given to all the patients investigated, one hour prior to surgery. In paper IV, the patients received light balanced, or moderately high-dosage fentanyl anesthesia, during nitroprusside infusion. Supplementary doses of the drugs were given in different proportions in the two groups studied. In the group receiving relatively high doses of fentanyl, the blood-gas analysis was carried out during, as well as after, the surgery and the values were compared with those obtained under light balanced anesthesia in a similar manner. Neostigmine 2.5 mg

and atropine 1.0 mg were used intravenously to reverse the effect of dTc at the end of the operation. Naloxone 0.2 mg was given intravenously to reverse the respiratory depressant action of fentanyl after surgery in those patients who were administered a higher dosage of the drug.

Doses of fentanyl given to the patients were high in papers II, III, IV and V. The average dosage for fentanyl was $16-20 \text{ ug. kg}^{-1}$ during a major operative procedure stretching over approximately two hours. Infusions of nitroprusside and trimethaphan were 0.01 and 0.1 per cent in strength, respectively and the drugs were mixed with an isotonic glucose solution. Halothane was made use of as an adjunct in paper I, II and IV. Droperidol was included in paper II only. The patients received Ringer acetate or Ringer lactate 1.0 l and fructose-glucose 1.5 l on the day of operation.

In paper V, intravenous nitroglycerin, in a 0.01 per cent solution in isotonic glucose, was added to the list of other two hypotensive agents-- nitroprusside (0.01 per cent) and trimethaphan (0.1 per cent) which were administered during deep analgesia with fentanyl. The control group received only high dosage fentanyl anesthesia and were subjected to surgery under normotension.

RESULTS AND COMMENTS

Controlled hypotension in hip joint surgery: An assessment of surgical hemorrhage during sodium nitroprusside infusion (I)

On measuring the surgical hemorrhage under the light balanced anesthesia intraoperatively in normotensive and hypotensive patients, it was noted that the amount of blood loss was reduced very significantly (43) during intentional hypotension (Fig. 3). Comparing the results with those obtained under regional anesthesia (44), the reduction in the surgical hemorrhage was also found to be considerable.

The postoperative assessment of the blood loss indicated insignificant differences in the two groups investigated. Fig. 4. illustrates the comparison between the results of this investigation with those of the other authors (44-46). There was no apparent difference seen in the bleeding after epidural blockade when compared with the data presented herein.

The total blood loss seemed to have decreased remarkably during surgical ischemia, whereas the difference between the hemorrhage under elective hypotension diminished significantly when it was compared with the epidural anesthesia. Under deliberate hypotension a moderate reduction in the operating time was observed. The blood transfusions during arterial hypotension were reduced sufficiently, on the whole, as the intraoperative replacement of the blood was not warranted in any of the patients submitted to intentional surgical ischemia. A moderate, but transient fall in the arterial pO_2 was encountered in a few patients during sodium nitroprusside administration. Such reductions are in agreement with an investigation conducted by other workers (47).

Summarizing the results obtained during an average of 80 minutes of SNP infusion, with the exception of a few cases showing a transient pulmonary hypoxic response, and excessive tachycardia in one patient treated successfully with the beta receptor blockade, no untoward side

CHANGES (%)

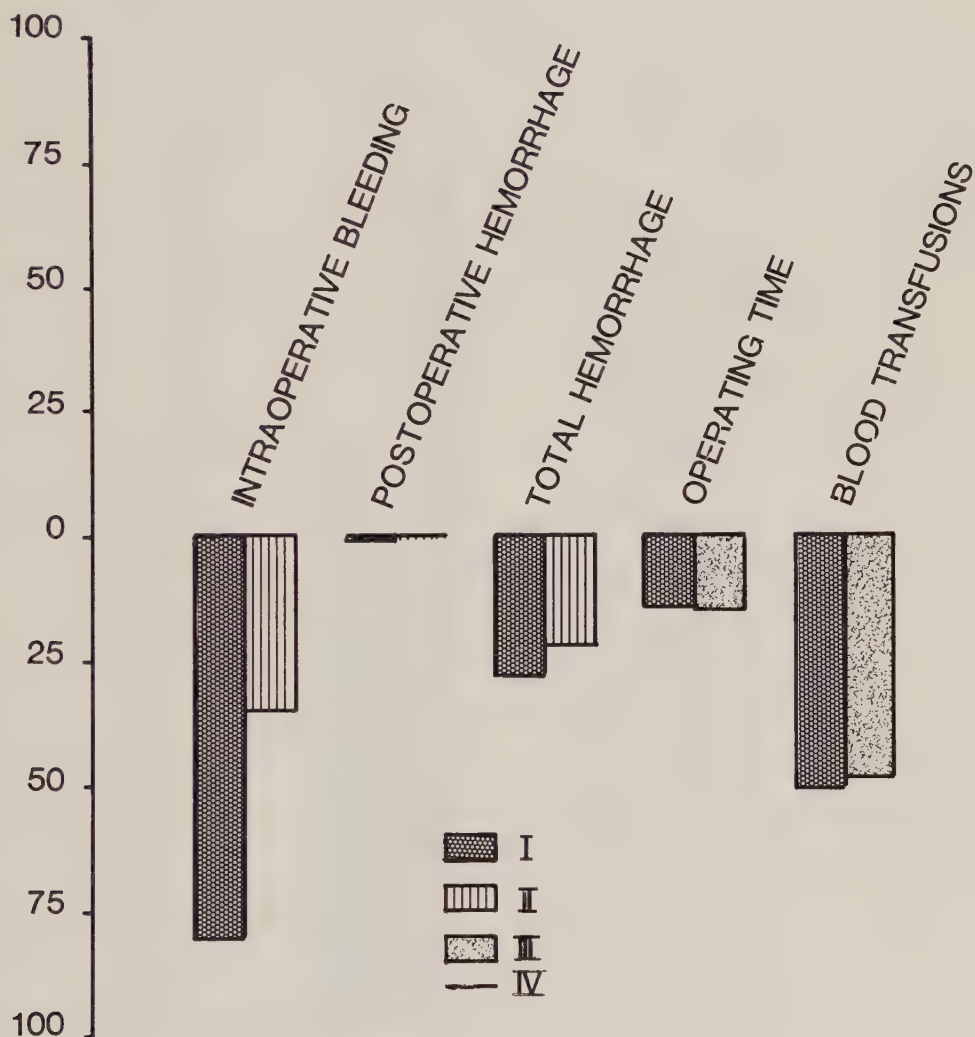


Fig. 3. Comparison of reductions in mean hemorrhage between controlled hypotension (I), and epidural anesthesia (44); and comparison of operating time and transfusions during unilateral (I), and bilateral (III) hip replacement under induced hypotension; — indicates no significant change (IV)

TOTAL HIP ARTHROPLASTY POSTOPERATIVE HEMORRHAGE (ml)

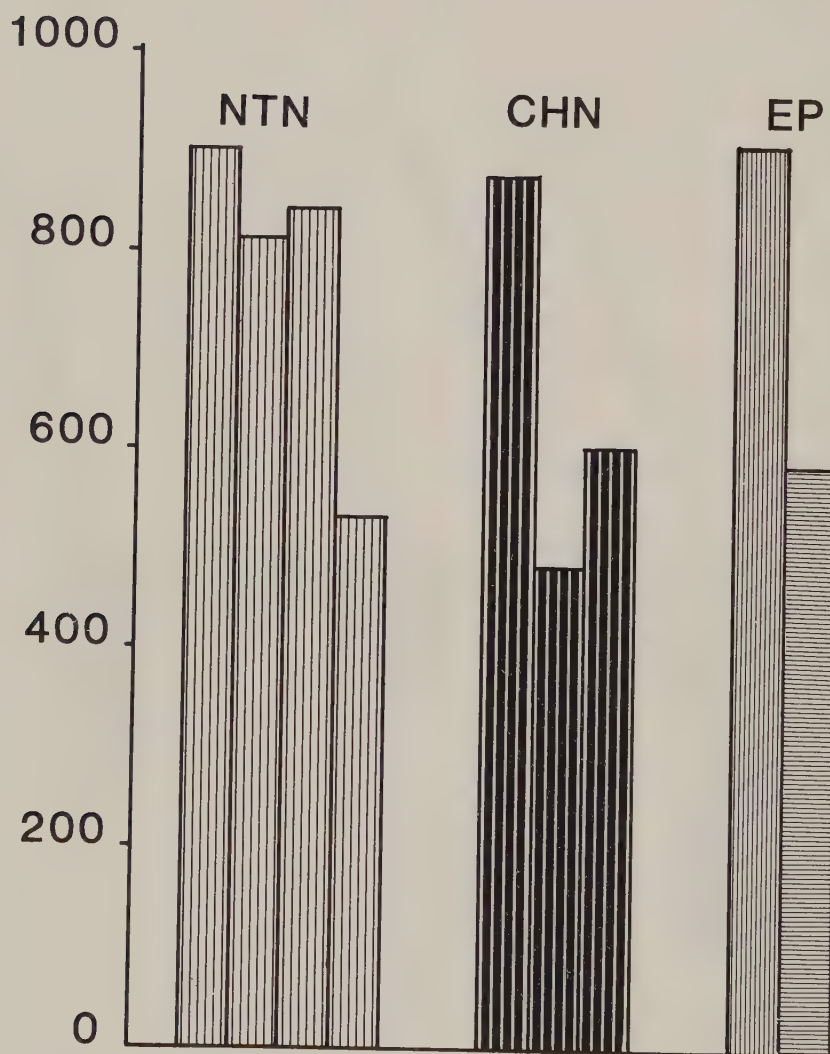


Fig. 4. Comparisons of means of postoperative bleeding during normotension (NTN, 43-46), controlled hypotension (CHN, 43-45,46), and epidural anesthesia (EP, 44,45);(by the permission of the authors)

effects of the hypotensive agent were observed. During a surgical operation stretching over a mean of 94 minutes, the only unusual observations were occasional moderate, but transient falls of the blood pressure under normotension upon the implantation of acrylic bone cement, whereas the alterations in the arterial pressure were not significant during nitroprusside administration with concurrent continuous monitoring of the mean arterial pressure. The incidence of a delayed postoperative diuresis was frequent in the two groups studied.

Deliberate arterial hypotension in plastic surgery for the reduction of hypertrophic breast: A critical appraisal of surgical ischemia and hemodynamic changes during sodium nitroprusside infusion (II)

In the investigation during surgery on the hypertrophic breast the various measures entailed the assessment of blood loss under normotension and deliberate ischemia produced by trimethaphan (TMP) or sodium nitroprusside (SNP). A considerable reduction was seen in hemorrhage under hypotension induced by TMP or SNP, during the removal of an average of 1100 g of fat tissue when it was compared with the surgery under normotension. The difference in the postoperative bleeding of the three groups was nonsignificant. No blood transfusion was required during the intentional hypotension.

Subsequent to a moderate reduction in the mean arterial pressure (31 %) during nitroprusside infusion, there was a marked diminution both in the central venous pressure and the peripheral vascular resistance (Fig.5) when compared with the control (pre-SNP) values. The decreased levels were restored towards the baseline values after the discontinuation of the hypotensive agent, and were nearly at par with them. The heart rate (HR) increased moderately, thereby causing a rise of cardiac output (CO) as well as the limb blood flow (LBF) during the SNP administration. These parameters returned to control or near-control levels in the postoperative period after the interruption of SNP. There were minimal increments seen

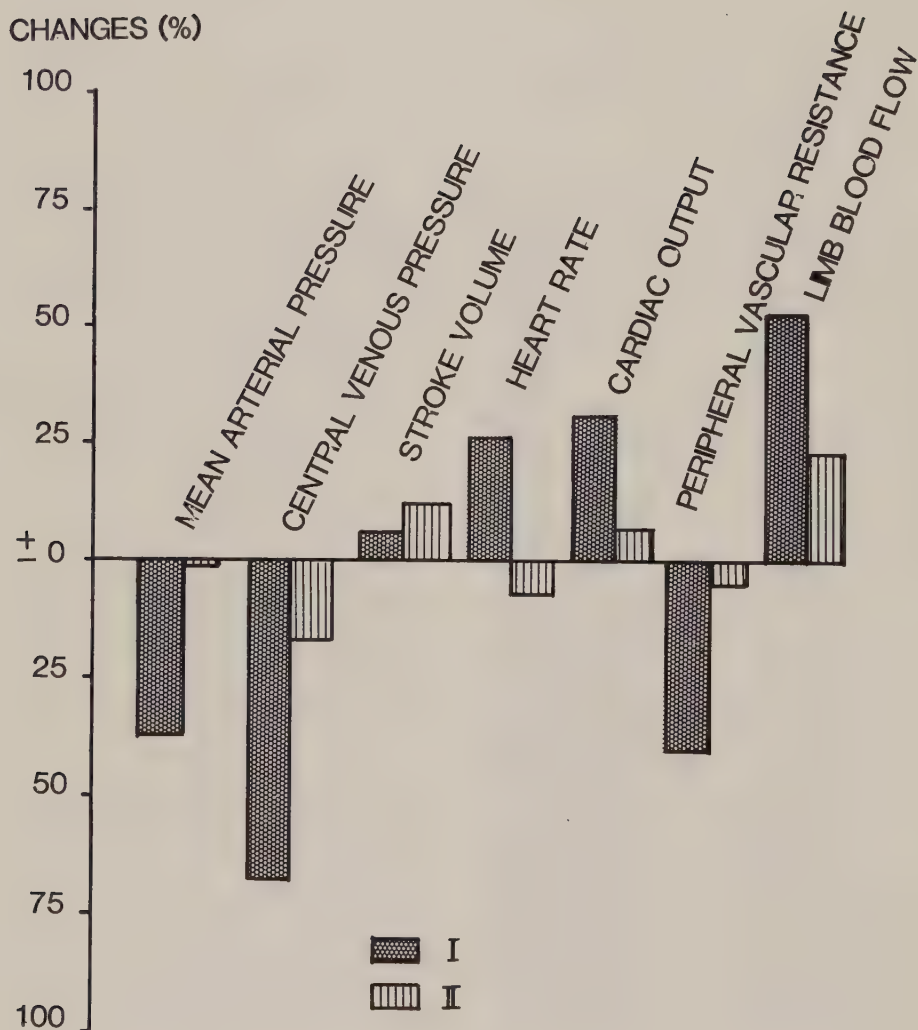


Fig. 5. Mean changes in hemodynamic measurements during sodium nitroprusside (SNP) infusion (I), and postoperatively (II); 0, indicates control (pre-SNP) values.

in the ventricular stroke volume (SV) in the both phases (Fig. 5). The SV, CO and the LBF rose significantly under the SNP infusion and there was an evidence of their levels remaining elevated modestly even at the recovery room (approximately 3 hours after the commencement of SNP infusion). The changes seemed to be greater in their magnitude when compared with the alterations in the same hemodynamic parameters during the employment of nitroprusside in patients of higher age (III). During the infusion of TMP, the need for accessory halothane became frequent to maintain the desired low levels of the mean arterial pressure (MAP). The requirement for halothane as an adjuvant was obviated during SNP administration, thereby indicating that the tachyphylaxis is probably encountered only during TMP application. The increase in the CO during SNP infusion which is commonly attributed to the tachycardia, and observed in this study is in accord with other published reports on its hemodynamics (48-51). There was a total lack of excessive tachycardia which may be ascribed partly to the administration of high doses of the neuroleptic drugs. The sporadic incidence of a slight disturbance of vision after TMP infusion was found to be a temporary phenomenon. It was thought to have been caused by the pupillary dilatation. Such a parasympathetic activity has been demonstrated in experimental animals after arfonad infusions (52). The occurrence of a persistent hypotension seen occasionally in the postoperative period by other investigators (53) was nonexistent in the patients studied herein; although it may have been due to the fact that these patients were younger and in good general condition.

The noninvasive method of measuring a number of hemodynamic changes by the bioelectric impedance plethysmography, proved very convenient in patients who were awake or anesthetized and undergoing surgery. The repeated monitoring provided a constant watch over the changes occurring in the cardiac function of patients during SNP infusion.

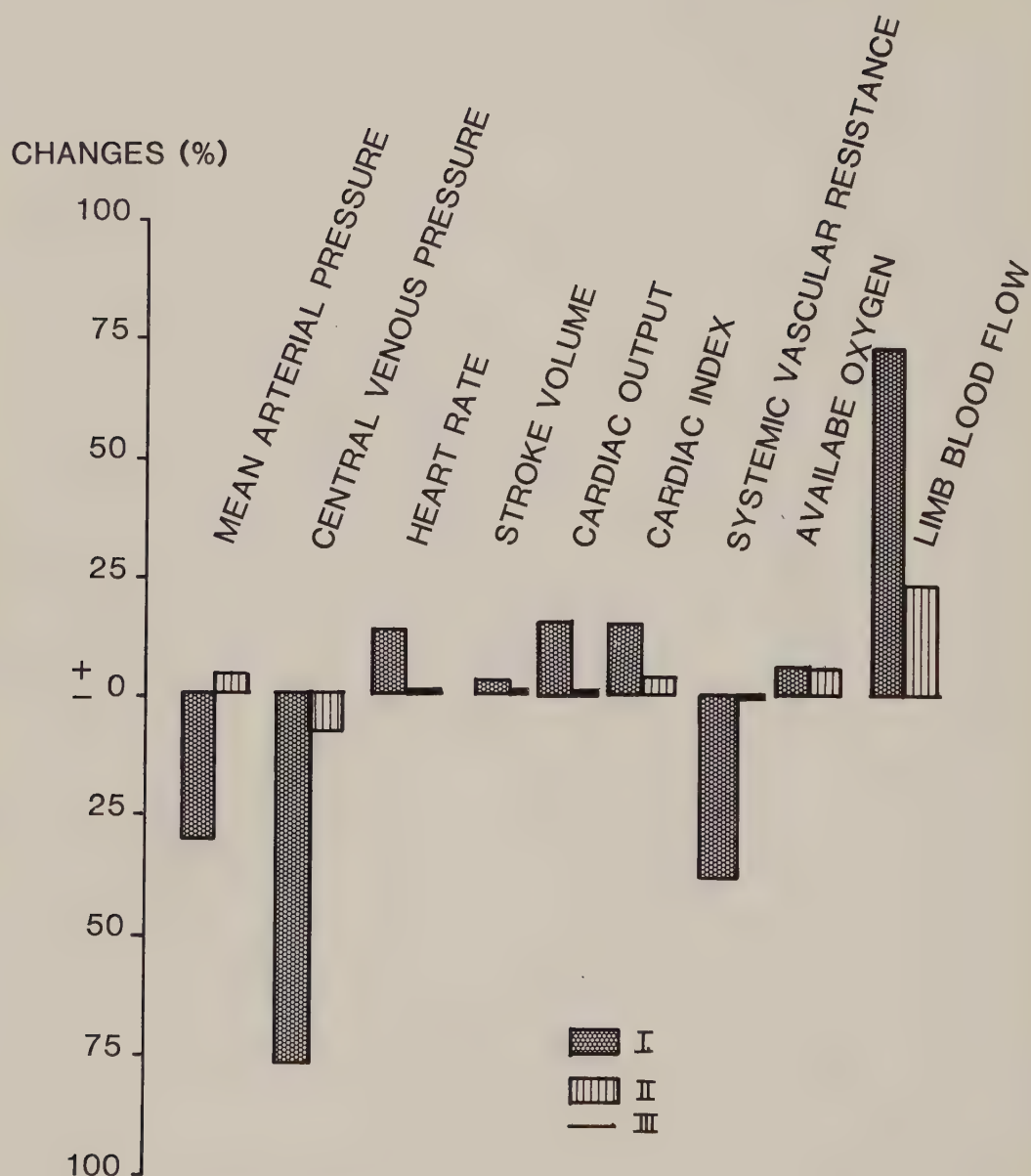


Fig. 6. Mean changes in hemodynamic parameters during sodium nitroprusside (SNP) infusion under hip arthroplasty (I), and postoperatively (II); 0, denotes the baseline (pre-SNP) values. Insignificant changes (III).

Hemodynamic changes during nitroprusside and trimethaphan infusions with concurrent moderately high dosage fentanyl anesthesia: An invasive and noninvasive study during hip arthroplasty (III)

The impact of moderately high doses of fentanyl on human dynamics was studied during minimal infusions of trimethaphan (TMP) or sodium nitroprusside (SNP). The induction of arterial hypotension which involved a moderate reduction of the mean arterial pressure led to a rise of heart rate (HR) in the both groups of patients (Fig. 6,7). The pre-hypotensive levels of the various parameters served as controls. During hypotension produced by SNP, a significant increase in the cardiac output (CO) was ascribed to a raised HR as well as a minimal increase in the stroke volume (SV). On the contrary, there was a consistent and significant diminution of SV during TMP administration; but the rise of HR being greater in magnitude, the resultant CO seemed to be well maintained.

The cardiac indices during the infusions of SNP or TMP, were well preserved (Fig. 10). On the discontinuation of the hypotensive agents the HR returned to the values approximating the controls. The fall in the central venous pressure and the calculated peripheral vascular resistance was considerable under the two infusions, and were restored to near-baseline levels on the cessation of the infusions. A marked rise in the limb blood flow was noted in all the patients submitted to deliberate hypotension and it remained elevated moderately in the postoperative period, after the interruption of SNP. The magnitude of increase in the SV was small when compared with their younger counterparts, whereas the changes in the limb blood flow were not very different in the two groups of patients investigated (Fig. 5,6).

The prominent features of this study included an almost total lack of the sudden fluctuations in the arterial pressure during SNP infusion or after its discontinuation, which is in discord with the experience

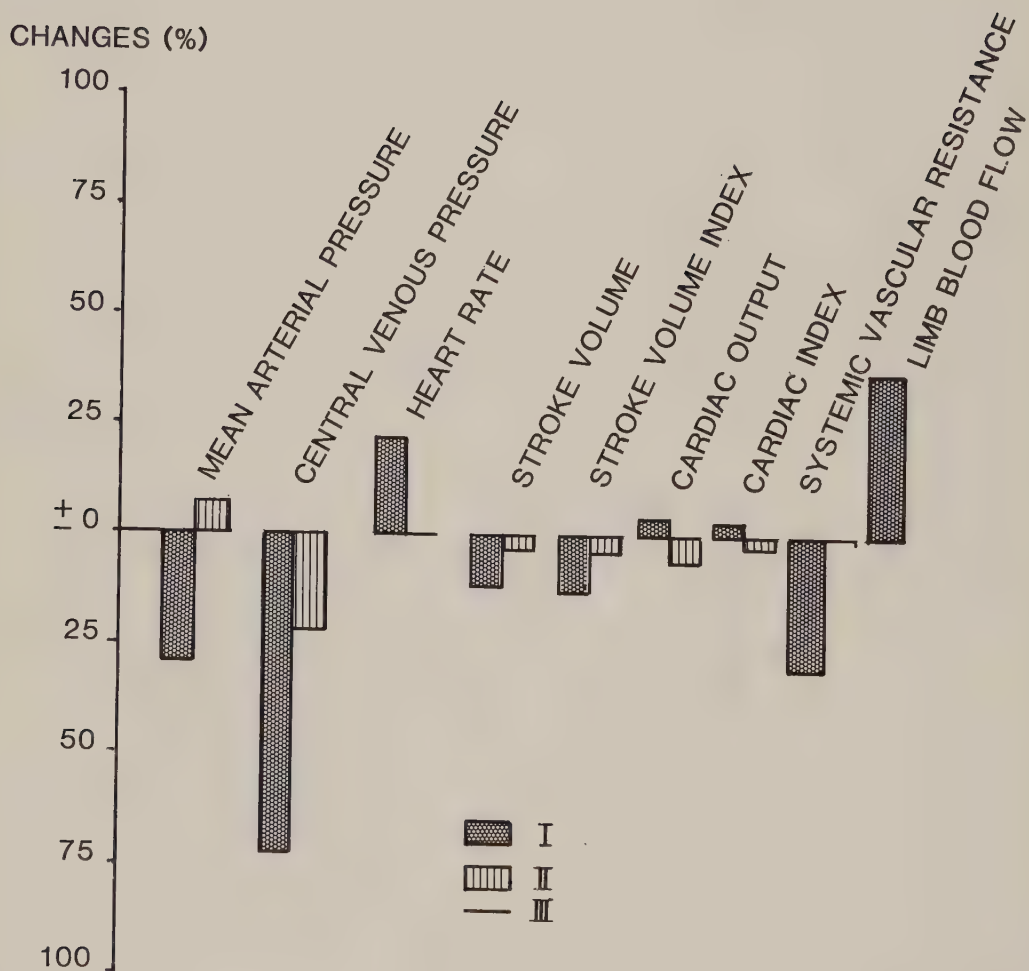


Fig. 7. Mean changes in cardiovascular dynamics during trimethaphan (TMP) infusion (I), and postoperatively (II); 0, indicates control (pre-TMP) values. Insignificant changes (III).

of other workers (54, 55). An abrupt alteration in the heart rhythm was also absent. An initial rise in HR may as well have been caused by the high induction dose of d-tubocurarine, while a moderately high dose of fentanyl appeared to have partially suppressed the consistent reflex sympatho-adrenal stimulation in response to the constant surgical activity.

The electrocardiographic monitoring revealed an absence of detrimental effects of the hypotensive agents on the myocardial contractility in minimal infusions. Sporadic but transient changes in ECG seemed to be linked directly with the higher doses of the two hypotensive agents administered. A rare incidence of ST segment depression but a more frequent occurrence of the T wave changes has been observed by Simpson (56) while Fahmy (16) found a more frequent, but transient incidence of the electrocardiographic changes suggestive of ischemia, although the total dosage of SNP administered, in both these studies was not specified.

Sodium nitroprusside as a hypotensive agent in surgery: Determination of the minimal dosage requirement with moderately high doses of fentanyl (IV)

In this investigation a mean dose of $18 \mu\text{g. kg}^{-1}$ of fentanyl seemed to have reduced the dosage requirement of sodium nitroprusside for attaining the desired low levels of MAP (60-65 mmHg) from 0.69 mg. kg^{-1} or $8.5 \mu\text{g. kg}^{-1}\text{min}^{-1}$ to 0.3 mg. kg^{-1} or $3.6 \mu\text{g. kg}^{-1}\text{min}^{-1}$. The accessory moderate concentrations of halothane became mandatory in the control group (light balanced anesthesia), whereas during the administration of a deep fentanyl anesthesia produced by moderate doses of fentanyl, N_2O and curare, the necessity to use the supplementary inhalation agents was circumvented entirely. The respiratory apnoea was seen predominantly at the end of surgery, thereby making the use of naloxone essential for

Table 1. Comparison of Minimal Doses of Sodium Nitroprusside (SNP) with Lethal and Suggested Doses.

Reference	Various Dosages of SNP (mg. kg ⁻¹)	Rate of Infusion (μg. kg ⁻¹ . min ⁻¹)
<u>Lethal dose</u>		
MacRae and Owen (60)	4.2	46.6
Jack (62)	11	366
Merrifield & Blundell (61)	6 (2 mg. kg ⁻¹ hr ⁻¹)	33
Davies et al (63)	10	125
McDowall et al (58)	4.2	70
<u>Suggested dose</u>		
Editorial (59)	3 (per hour)	50
Vesey et al (57)	1.5	12-13
<u>Minimal dose used</u>		
Vazeery et al (IV)	0.3	3.6

reversing this side effect in all patients. No further naloxone was ever needed at the recovery room.

The blood-gas analysis conducted intermittently during SNP infusion, revealed a frequent incidence of pulmonary hypoxic response in low dosage fentanyl (higher amount of SNP) anesthesia. Its occurrence as well as magnitude was reduced very significantly under the high dosage fentanyl administration (minimal infusion of SNP). The difference in magnitude appeared to be related directly to the amount of nitroprusside given.

Estimations of sodium thiocyanate in serum showed an initial elevation in the two groups--the magnitude of rise being steeper in the higher dosage SNP (control) group, whereas the subsequent estimations revealed no significant differences in the two groups studied.

Vesey et al (57) suggested not to exceed a maximum dose of 1.5 mg. kg^{-1} or $13 \text{ ug. kg}^{-1} \text{ min}^{-1}$ in view of the estimations of thiocyanate and cyanide in serum under SNP infusions, thereby repudiating the recommendations made previously by other researchers (58,59). (Table 1). A dosage of $1.1\text{--}7.4 \text{ ug. kg}^{-1} \text{ min}^{-1}$ appears to be a reasonable alternative under moderately high dosage fentanyl anesthesia, and complies eminently with the recommendations of the aforementioned authors (57). It certainly eliminates the fears of the very many clinicians who are aware of the mishaps that occurred inadvertently (60-63).

Changes in cardiac output and systemic blood pressure after insertion of acrylic cement during trimethaphan, sodium nitroprusside and glycerol trinitrate (nitroglycerin)-induced hypotension: A comparison with changes during normotension (V)

On insertion of the acrylic bone cement the cardiocirculatory response was variable in the 4 groups of patients studied (Fig. 8). A significant fall in the mean arterial pressure (MAP), after a potential

IMPLANTATION OF ACRYLIC BONE CEMENT

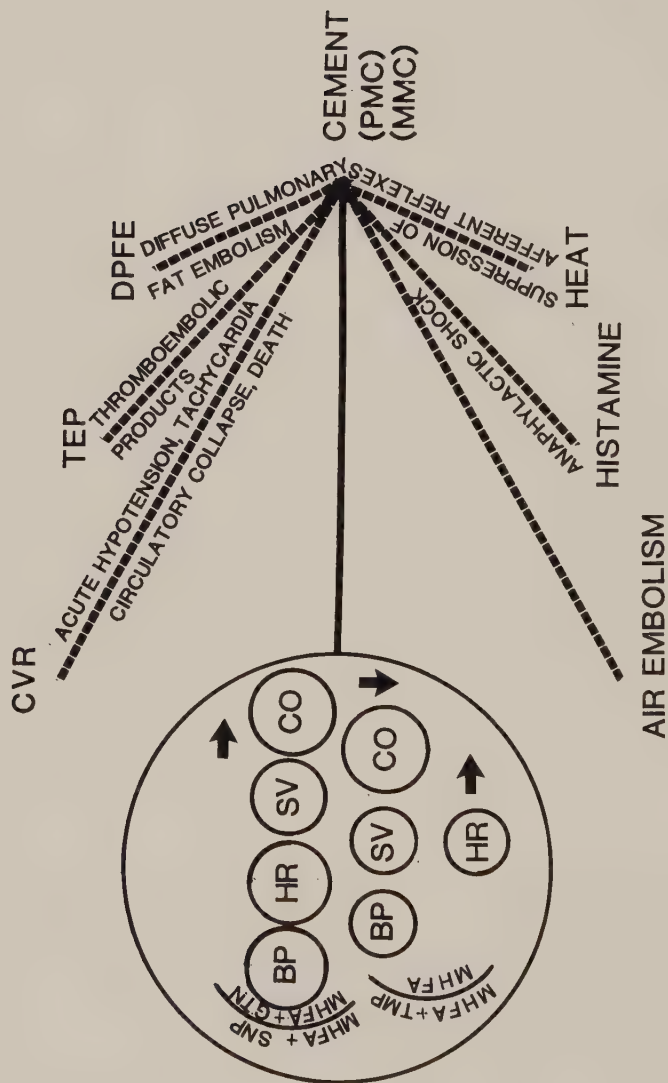


Fig. 8. Published reports of hazards on insertion of acrylic bone cement. CVR, cardiovascular response; MHFA, moderately high dosage fentanyl anesthesia; TMP, trimethaphan; SNP, sodium nitroprusside; GTN, glycerol trinitrate; BP, blood pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; PMC, polymeric methylmethacrylate; MMC, monomeric methylmethacrylate.

absorption of the monomer was encountered frequently both after the acetabular and femoral implantation of the cement under normotension and trimethaphan (TMP)-induced hypotension. The alterations of MAP during hypotension produced by sodium nitroprusside (SNP) or glycerol trinitrate (GTN) were nonsignificant.

There was no abrupt change seen in the heart rhythm in any of the patients included in this study. Moderate reductions of stroke volume (SV) were noted during normotension as well as TMP-induced hypotension. The fall in the SV, and hence a diminished cardiac output (CO) was transient. These parameters were restored to the baseline values after a short span of 8-10 minutes.

The changes in the MAP were partly in accord with those of other workers (64-67) under normotensive anesthesia or hypotension induced by TMP. Observations made during the elective ischemia produced by SNP or GTN, failed to reveal alterations of any significance in the MAP. Subsequent to the application of methylmethacrylate in the reamed surface of acetabulum or the medullary canal of the femur, there have been variable reports of either an increase in HR with an accompanied hypertension (66) or an associated hypotension caused probably by its vasodilator action (65). The arterial hypotension caused by a peripheral vasodilator leads usually to a compensatory increase in HR and CO. The findings presented herein are in contradistinction to those depicted by these various authors(64-67). A consistent HR with associated nonsignificant changes in the MAP and the CO, on insertion of the acrylic material under the infusions of the pure vasodilators, suggests that the monomer may have a potent vasodilator component in itself. It also eliminates sufficiently the probability of the peripheral vasodilator action of the acrylic monomer being mediated through the release of histamine.

GENERAL DISCUSSION

In the present age of an industrious, invasive and noninvasive monitoring of the patients, the essential clinical manifestations can be interpreted promptly, and any potential untoward effect of a drug or a clinical method may easily be obviated (68-73). In the light of an exhaustive information available through a number of investigations conducted over the last 30 years, there is a little doubt now that the massive blood transfusions given to the patients undergoing major surgical interventions, are most likely amongst the precipitating causes of the ensuing complications (75-77). It seems likely that the controlled arterial hypotension may either attenuate the severity or reduce the magnitude of these potential sequelae by curtailing the need for the excessive transfusions.

In the various investigations conducted our efforts encompassed a number of reconstructive orthopedic or plastic surgical procedures, although most of the clinical work embraced the elective surgery for the total replacement of the hip joint. The attempts to diminish the bleeding, and thereby accomplishing very often a total exsanguination of the operating field, appeared to bring about gratifying results. Many other workers have been engaged in similar efforts to facilitate surgery for a total hip arthroplasty. The amount of intraoperative blood loss during our investigation (I) has been compared with the results of a few recently published works (Fig. 9) (43-45,74). Although the application of the hypotensive agents in association with the inhalation agents, appears to be another alternative, and is a commonly practiced method for inducing the surgical ischemia, we would have preferred a method where the patients were awake at the end of surgery and capable of communicating with the physician or the nurse looking after him at the recovery room.

The current introduction of the pure vasodilator drugs in hypotensive

HIP REPLACEMENT ARTHROPLASTY

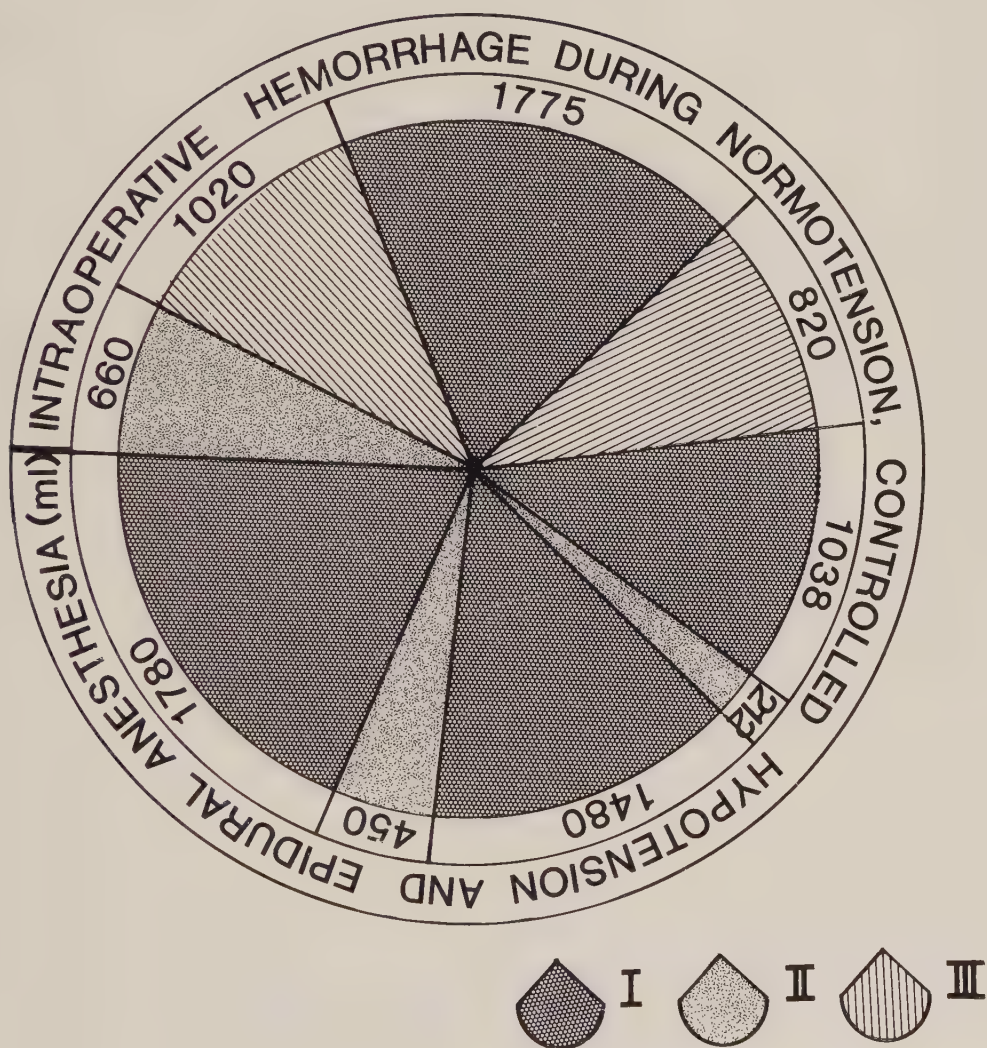


Fig. 9. Comparison of intraoperative hemorrhage (I), with published reports. Beginning clockwise at 3 O' clock, Vazeery & Lunde (43); Lawson et al (74); Rosberg et al (45); Jakobsen & Wigren (44). I, indicates normotension; II, controlled hypotension, and III, epidural anesthesia.(With the permission of the authors)

anesthesia has practically eliminated the incidence of the previously encountered pitfalls, namely-the postoperative hematoma formation or the frequent occurrence of a persistent hypotension. We did not come across with any case where such a haphazard may have directly been related to the use of the elective hypotension.

During the surgery on the hypertrophic breast and the degenerative disease of the hip, the manipulation of the hypotensive technique was frequently associated with a moderate tachycardia under the infusion of SNP or TMP. An excessive increase in the heart rate was nearly unknown. The potential effects of a vagal withdrawal leading to tachycardia can be reduced significantly via the beta receptor blockade (78). Moderately high doses of fentanyl appeared to have prevented the rebound hypertensive episodes seen after the discontinuation of SNP, which have been depicted by a few investigators (54,55). The explanation lies probably in the fact that the high doses of fentanyl may substantially suppress the baroreceptor response both during and after the administration of nitroprusside.

The vital correlates of myocardial function, namely-- the ventricular stroke volume, cardiac output, peripheral blood flow and the cardiac index, invariably determine the beneficial or the detrimental effects of a therapeutic agent. The positive inotropism demonstrated by TMP and SNP, during our investigations is generally in accord with the observations of other workers (79,80). It appeared to be a combination of both a ganglionic blockade and a vasodilatation in the case of the former, whereas a pure vasodilatory effect being demonstrated by the latter. The cardiac indices were well preserved in a great majority of the patients studied, and on comparing the results during the two hypotensive agents employed (III), a good correlation was seen (Fig. 10).

The incidence of tachyphylaxis was frequent during arfonad infusions in the younger age group of patients, but was virtually nonexistent

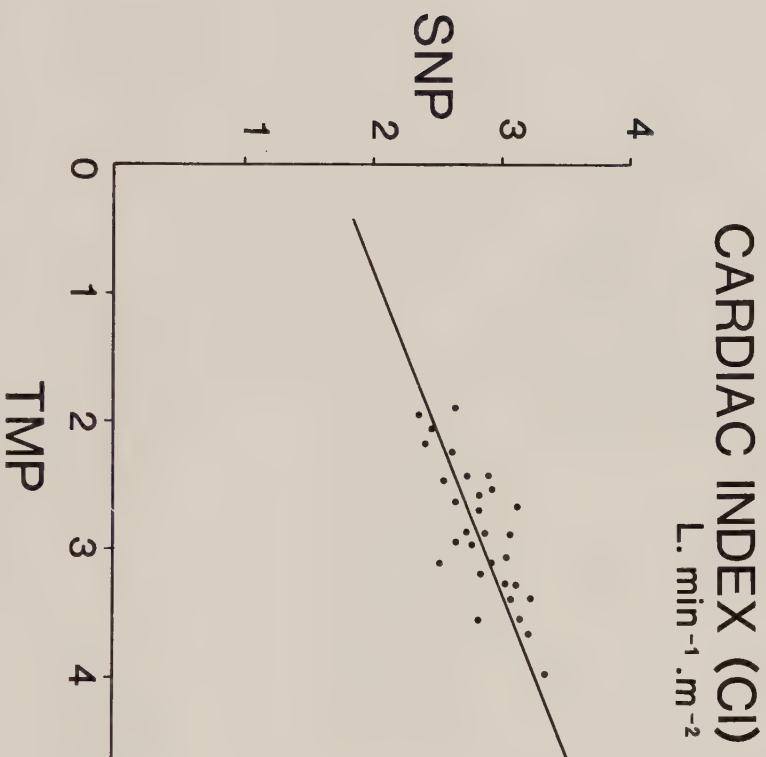


Fig. 10. Correlation between the cardiac indices obtained during sodium nitroprusside (SNP), and trimethaphan (TMP)-induced hypotension under moderately high dosage fentanyl anesthesia. ($r = 0.913$, $P < 0.001$)

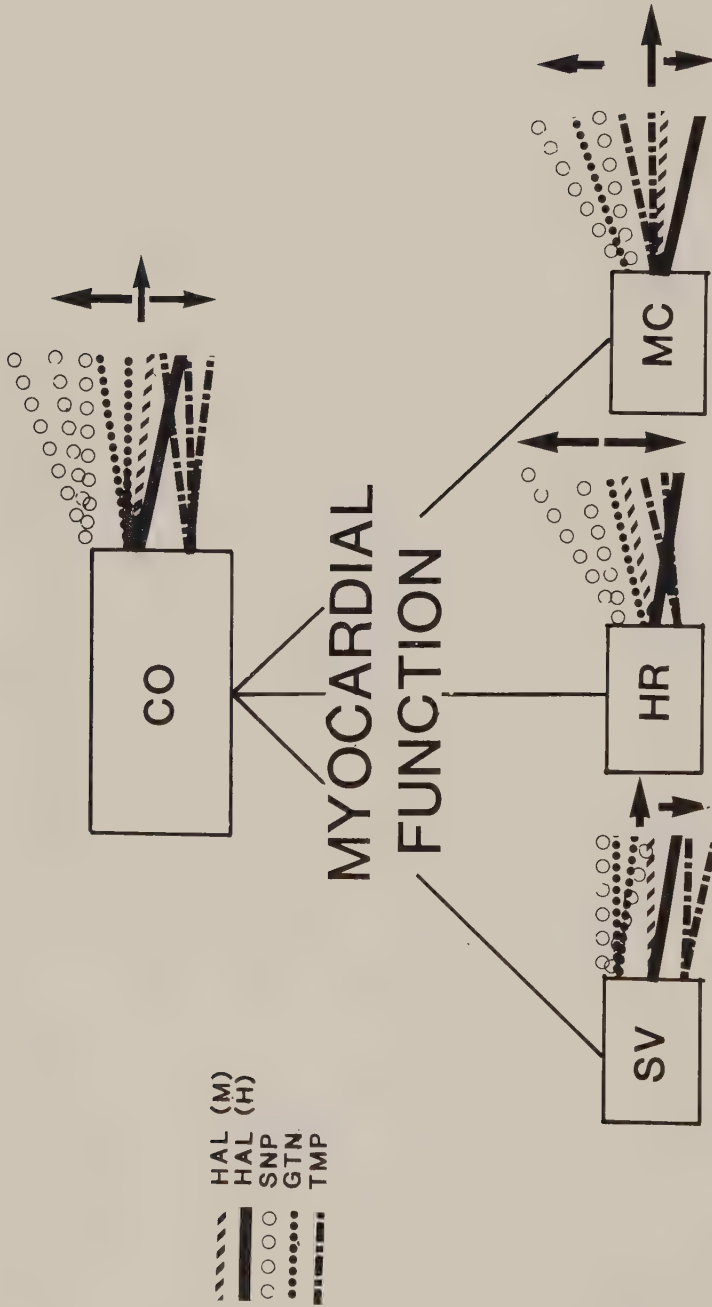


Fig. 11. Effect of the commonly employed hypotensive agents in surgery; trimethaphan (TMP), sodium nitroprusside (SNP), glycerol trinitrate (GTN), and halothane on heart. HAL (M) indicates minimal and HAL (H), the high concentrations of halothane. CO, cardiac output; SV, stroke volume; HR, heart rate; MC, myocardial contractility. $\uparrow$ denotes an increase, $\downarrow$ a decrease and $\rightarrow$, nonsignificant change

during nitroprusside. The general consensus about TMP regarding its ability to improve the regional blood flow is based on an inherent character of the sympathetic and the parasympathetic inhibition (81-86), and a weak vasodilator action which is thought to be mediated through the release of histamine (12, 87).

During studies under elective hypotension procured by SNP, a consistent and moderate increase in the cardiac output with a concomitant tachycardia was a frequent observation by us. The hemodynamic response to its application represents a combination of venous pooling and reduced arterial impedance (88,89). The peripheral vasodilatation is thought to be brought about via an apparent arteriolar dilatation during studies on experimental animals (4,90). Human studies on normotensive and hypertensive individuals failed to demonstrate an arterial dilatation although it does reduce the calculated total peripheral resistance (91) (Fig.11 illustrates the effect of hypotensive drugs on heart).

The improvement in left ventricular performance during SNP infusion under high dosage fentanyl administration was in agreement with the findings of other workers who employed it in combination with the inhalation agents (49,50). Nitroglycerin (GTN) which was introduced recently in anesthesia (16), has been known to improve coronary circulation for over a century (92). The intravenous administration of GTN appears to be of immense value in reduction of blood pressure in the postoperative care of heart patients (93,94). The return of arterial pressure to baseline values appears to be slower than SNP, and explains a comparatively less evanescent character than that of the latter.

Halothane with oxygen alone diminishes the contractile force of heart, stroke volume and the cardiac output (95). In their studies on human beings Prys-Roberts and his associates found nonsignificant changes in the total peripheral vascular resistance while it was revealed that halothane had a definite dose-related depressive action on human heart

(96,97). In studies on dogs, Ahlgren et al encountered a significant depression of left ventricular function, while the left heart function during hemorrhagic hypotension improved (98). Halothane proved to be a valuable adjunct in a number of our patients. It helped to potentiate the hypotensive effect of other drugs, or assisted in obtaining a better control of arterial ischemia.

The muscle relaxant d-tubocurarine (dtc), when used in combination with halothane, is known to potentiate the ganglion blockade, and the moderate tachycardia seen in the patients could have been caused by an initial high dose of dtc (25-30 mg), and it may as well have contributed significantly towards hypotension.

In man, $10 \mu\text{g. kg}^{-1}$ of fentanyl significantly increases the ventricular stroke volume and the cardiac output (99) (Fig. 12). Moderately high doses of fentanyl ($15\text{-}20 \mu\text{g. kg}^{-1}$) during minimal infusions of the vasodilator drugs provided a high degree of cardiovascular stability (II-V). Due to a consistent circulatory stability obtained with large doses of fentanyl ($10 \mu\text{g. kg}^{-1}\text{min}^{-1}$), in the dog (100,101) it has been employed as an alternative to morphine in heart surgery (102,103). After the application of high doses of fentanyl ($16 \mu\text{g. kg}^{-1}$), there is a little modification seen in the distribution of the regional blood flow (104). In patients with limited cardiac reserve, a sufficient amount of cardiovascular stability particularly during induction and endotracheal intubation has been demonstrated with fentanyl in doses of $60\text{-}70 \mu\text{g. kg}^{-1}$ (105,106). The side effects of opiod anesthesia in high dosage are the bradycardia and respiratory depression during or after the surgery. The bradycardia can be minimized with atropine (102) or with pancuronium (105). The frequent apnoea seen at the end of surgery can be successfully reversed with naloxone, the narcotic antagonist. Its efficacy in reversing opiod-induced respiratory depression in patients following anesthesia or drug overdose is well documented (107-111). The

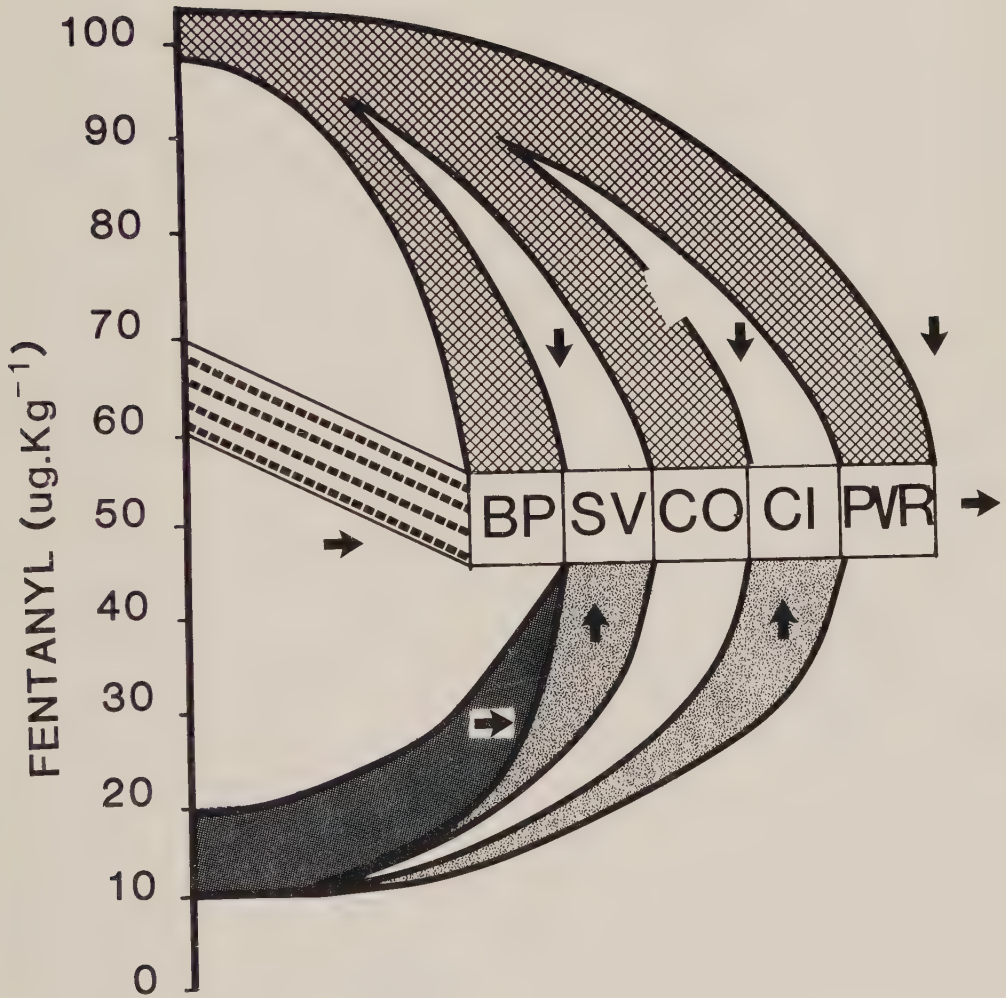


Fig. 12. Effect of different dosages of fentanyl on cardiovascular parameters. BP, blood pressure; SV, stroke volume; CO, cardiac output; CI, cardiac index; PVR, peripheral vascular resistance. $\rightarrow$, indicates stability or nonsignificant changes; $\uparrow$, denotes an increase, and $\downarrow$ indicates a decrease or depression.

delayed respiratory depression which may attend the administration of fentanyl (112) was unknown in the patients studied herein.

The prominent determinants of an essentially stable cerebrovascular dynamics are the cerebral blood flow (CBF), intracranial pressure (ICP) and the autoregulation of brain circulation (ARBC), and they seem to be interrelated and probably more so, interdependent on each other in order to maintain an efficacious circulatory function of cerebrum. The hypotensive agents currently in fashion in producing surgical ischemia may either increase, decrease or have no significant effect on the levels of these parameters (Fig. 13). A considerable amount of discrepancy is seen on studying the effects of these drugs on CBF, ICP and ARBC under induced hypotension. Trimethaphan may reduce the CBF (113) or cause nonsignificant alterations in it (114,115). It is thought to lead to a profound disruption or a loss of ARBC (116-118). Due to an evanescent character SNP is believed to impair the autoregulatory mechanisms in man (119,123) or animals (120). Fitch et al (121) found no evidence suggesting changes in ARBC under profound arterial hypotension with TMP or SNP, whereas the findings of others also support this view (118). It appears that TMP tends to maintain relatively constant ICP (118,122). During SNP-induced hypotension the changes in the ICP may occur abruptly in normocapnic patients, while the effect is not significant in hypocapnic individuals (119). The intravenous infusion of nitroglycerin seems to cause no increase in ICP due to the absence of marked swings of blood pressure (124). The ARBC seems to be well preserved when halothane is employed as an accessory with other hypotensive agents (122).

In the various studies conducted (II-V), the potential detrimental effects of the sudden fluctuations of systemic blood pressure during the hypotensive infusions were obviated apparently by administering moderately high doses of fentanyl concurrently.

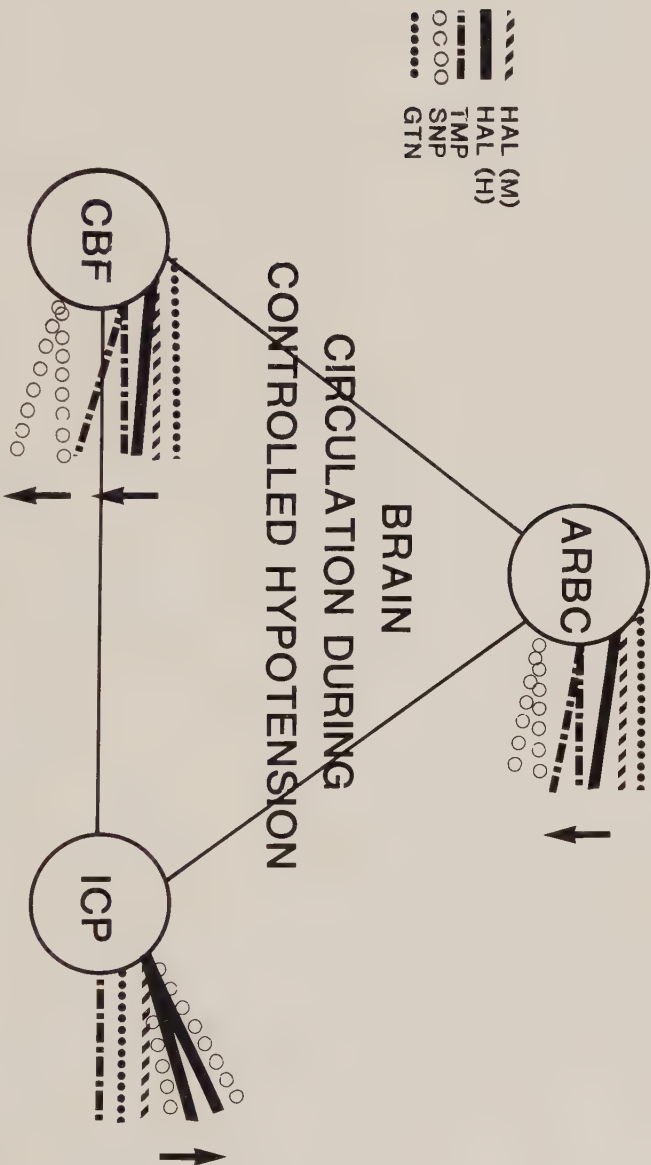


Fig. 13. Effect of the commonly used hypotensive agents in surgery; trimethaphan (TMP), Sodium nitroprusside (SNP), glycerol trinitrate (GTN), and halothane on brain circulation. HAL (M) indicates the minimal and HAL (H), the high concentrations of halothane. ARBC, autoregulation of brain circulation; CBF, cerebral blood flow; ICP, intracranial pressure. ↓ denotes a disturbance in case of ARBC, and a decrease in case of CBF. ↑ signifies an increase.

Kety and Schmidt demonstrated a marked reduction of CBF during profound hypocapnia (125) and there is evidence suggesting the existence of cerebral hypoxia during marked hyperventilation (126). Pronounced hypocapnia in the various investigations was avoided through routine blood gas analysis under deliberate hypotension.

The findings of Enderby (127) and Eckenhoff et al (128) do not suggest that mental deterioration commonly follows induced hypotension. In elderly patients similar conclusions have been reached by others during prostatectomies (129), and those whose patients were undergoing hip arthroplasties (43).

The renal diuresis which is either diminished or obtunded during the hypotensive technique invariably is restored to normal in the postoperative normotensive period (43,130-133). Other workers do not agree with this and imply that after ganglion blockade there is an overall vascular dilatation which restores the blood flow to control values despite continuing hypotension (134). This view may support the hypothesis of autotransfusion put forward by Converse and his colleagues (52). Hence it is very likely that, in the absence of vasoconstriction, the integrity of all tissues may be preserved adequately when blood flow is redistributed to the different organs despite a temporary dysfunction of one organ. Experimental studies conducted upon dogs during SNP-induced hypotension show a modest increase in renal blood flow (136). In similar experiments Wang and associates noted that nitroprusside either increased the renal flow, or maintained it well, during hypotension (137). These studies are supplemented by similar observations of others (138).

Electrocardiographic studies during SNP show frequent but transient changes in ST segments and T waves (16,56), whereas changes were scant as observed by others during minimal infusion of the drug (III). Nitroglycerin appears to be preferable as it does not cause any ischemic changes in human myocardium (16).

The elective surgery for the reconstruction of osteoarthritic hip joint involves the insertion of metallic prosthesis fixed in position with the acrylic bone cement. A small fraction of the liquid component of the cement or the monomeric methylmethacrylate, after the insertion of the cement into the reamed surface of acetabulum or the medullary canal of the femur, may be absorbed (139,140). It may, therefore produce a transient drop in the blood pressure, more commonly so after its insertion into the femoral canal. A number of alarming reports of a sudden profound hypotension (141-153), cardiovascular collapse (141, 142,144,154), or even sudden death have appeared in the literature (65, 141-144,155,156). The fall in the blood pressure is known to be transient, or it may lead to further cardiovascular collapss. During autopsies, widespread emboli of bone marrow, air or fat in the pelvic veins, lung, coronary arteries, kidney and brain were found (Fig. 14) (64,141-144,154-160), in cases where death followed immediately after the application of the cement. A moderate fall in the blood pressure soon after cement implacement into the acetabular cavity or the femoral canal, during normotension and TMP-induced hypotension in the study reported herein (V) is in agreement with the observations of some other workers (66,161); so are the similarities seen in the inconsistent change in the heart rate. However, our observations were in discord with others who did not see any change in pressure after acetabular insertion (64).

Controlled hypotension during hip arthroplasty was first advocated by Charnley (139) and thereafter nonsignificant changes in the blood pressure were reported by others (162). The reduction of the arterial pressure appears to be more obvious during the first 4 minutes following the implacement of the monomeric paste. Modig et al (67), during their investigations on patients undergoing Charnley's low friction hip replacement have demonstrated a more frequent existence of fat particles

CIRCULATORY PROFILE ON INSERTION OF CEMENT

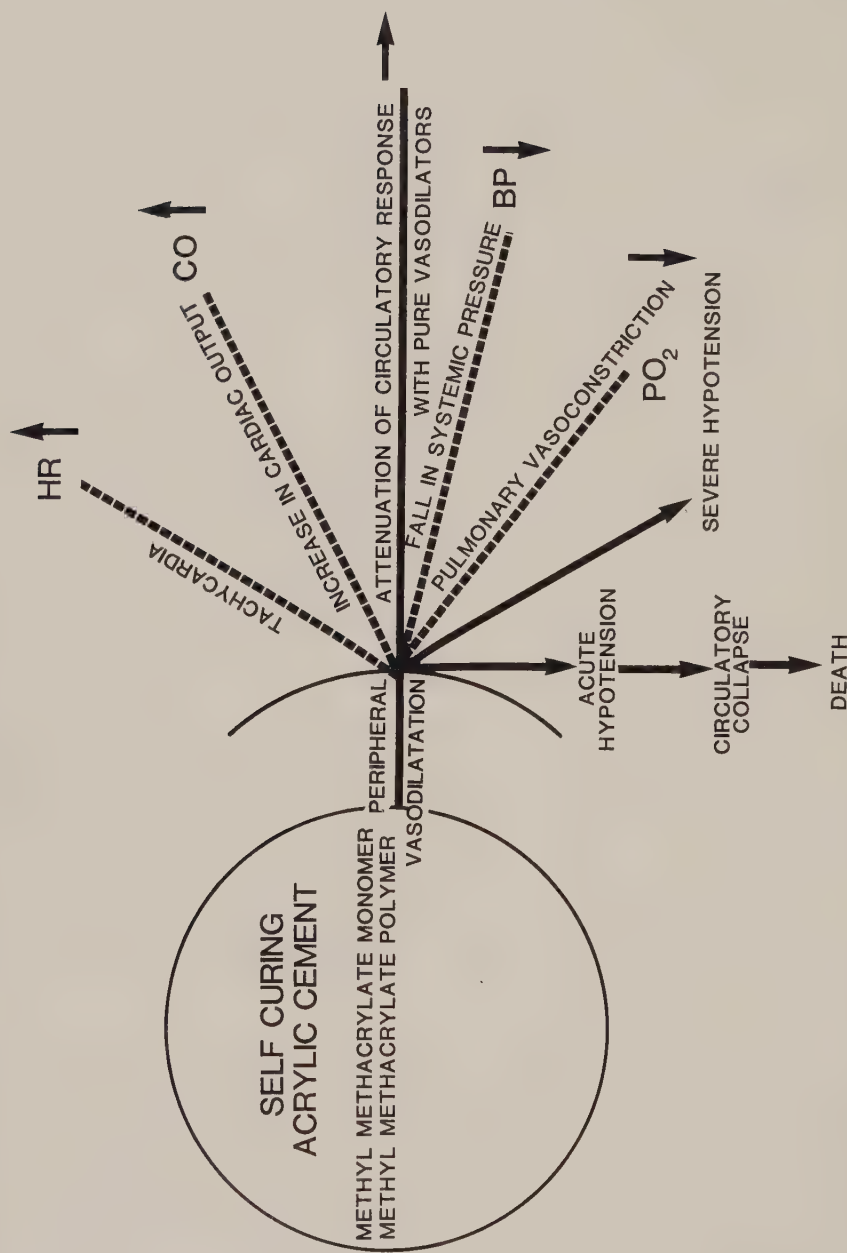


Fig. 14. A profile of hemodynamic response (V) to insertion of acrylic cement, and a comparison with published reports. HR, heart rate; CO, cardiac output; BP, blood pressure; PO₂, arterial tension. ↑, indicates an increase; ↓, a decrease, and →, denotes insignificant changes.

in the pulmonary artery immediately after the insertion of cement into the femoral medullary canal; thereby suggesting that the fat and other thromboembolic material from the bone marrow may contribute to the pulmonary and circulatory complications encountered sporadically under such an operation. Others have previously shown that fat embolism after the implantation of bone cement in the experimental animals is reproducible (163), while some have observed hemorrhagic changes following its insertion (158).

Studies on cardiovascular response after the application of acrylic material demonstrated a fall in pulse rate under halothane and no change during neuroleptanesthesia (164). An insignificant change seen in HR in all the 4 groups of patients (V), appears to be in line with the results reported by the aforementioned authors. There were no significant alterations in cardiac out (CO) after the insertion of cement during SNP- or GTN-induced hypotension, whereas moderate reductions of CO were noted during normotension or TMP-induced hypotension. Effect on CO was in contradistinction to the findings of Peebles et al (65), who encountered an increase in heart rate and CO during experiments on dogs, whereas the blood pressure response appeared to be similar. Hence it is concluded that the monomeric component of the acrylic cement most likely possesses a potent vasodilator action, and that this action is markedly attenuated during the administration of pure vasodilators namely-- sodium nitroprusside and nitroglycerin.

SUMMARY AND CONCLUSIONS

The results in this thesis show that:

1. Controlled arterial hypotension in the present era of diligent clinical monitoring is a method of choice during major surgical procedures involving massive unavoidable hemorrhages. The technique is easy to learn and conduct, and can contribute considerably towards better surgical treatment of a patient.
2. The enormous reduction in bleeding during intricate surgery and the total absence of the need to transfuse bank blood during a variety of major operations is evidence strong enough to propose such a method in essentially elective and cumbersome surgical manoeuvres. During a controlled and consistent surgical ischemia, the surgeons are provided with a better opportunity, during the reconstructive procedure, to show their skills and accomplish complementary results.
3. The evanescent profile of the currently available hypotensive drugs, trimethaphan, sodium nitroprusside, and nitroglycerin do not include any interactions during moderately high-dosage fentanyl anesthesia. The continuous monitoring of the patients' hemodynamics by noninvasive impedance plethysmography lacked any indications of such potential drawbacks. The prompt emergence from anesthesia at the end of surgery may support the argument against including inhalation agents as sole hypotension inducing means since their dose-dependent cardiodepressive actions are well recognised.
4. During high dosage fentanyl anesthesia, produced by $12-18 \mu\text{g. kg}^{-1}$ fentanyl, the optimal dosage requirement of sodium nitroprusside is substantially reduced, based on results of comparative hemodynamic and biochemical investigations. A dose of $2-6 \mu\text{g. kg}^{-1} \text{ min}^{-1}$ of nitroprusside or nitroglycerin, in combination with deep fentanyl anesthesia, will suffice to produce deliberate ischemia in a variety of operations stretching over a period of approximately two hours (Fig. 15).

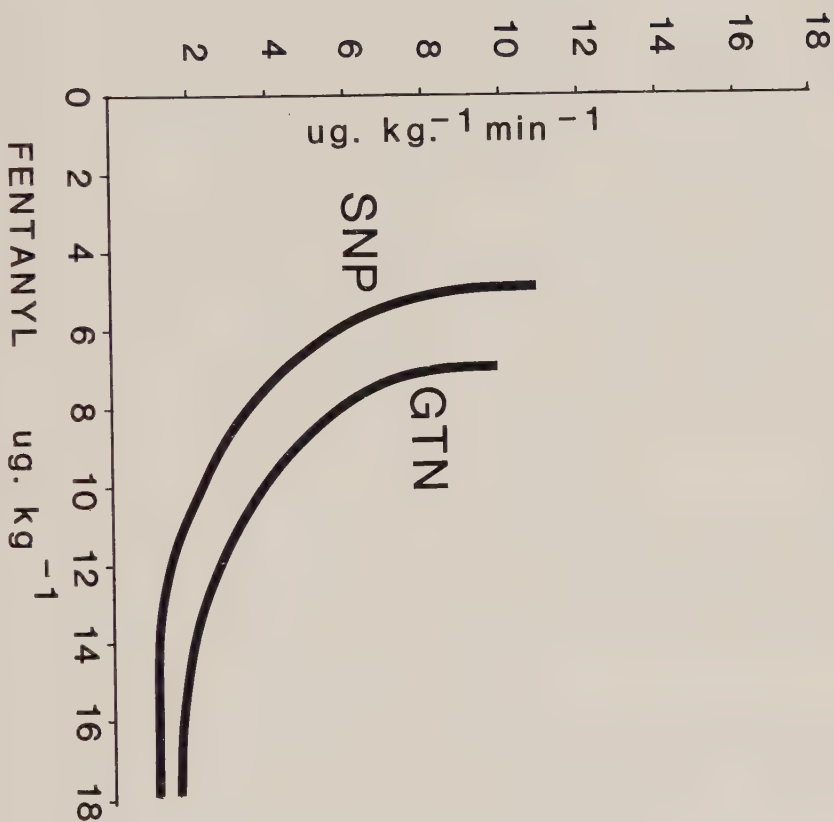


Fig. 15. Relationship between the rates of infusion of sodium nitroprusside (SNP), or glycerol trinitrate (GTN) during low and high dosage fentanyl anesthesia.

5. The results of the investigation show that the method is more effective in surgical intervention in the higher age groups of patients.
6. The sporadic side effects of the hypotensive drugs are temporary, and not very different from those of the several other drugs commonly employed in clinical anesthesia. Symptomatic treatment always eliminated the minor unpleasant side effects.
7. During induced hypotension in hip arthroplasty there was no evidence to suggest any significant cardiocirculatory depression, which may be encountered after the insertion of acrylic cement under normotension.
8. Absence of large fluctuations of arterial pressure, and the so-called rebound hypertension reported in the anesthetic literature after the discontinuation of the short-acting hypotensive agent (nitroprusside), was a consistent observation during moderately high-dosage fentanyl anesthesia.

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CONTROLLED HYPOTENSION IN HIP JOINT SURGERY

An Assessment of Surgical Haemorrhage During Sodium Nitroprusside Infusion

A. K. VAZEERY & O. LUNDE

Department of Anaesthesiology and Department of Orthopaedic Surgery, Central Hospital of Rogaland, Stavanger, Norway

Controlled hypotension, combined with light balanced anaesthesia, was employed during total hip replacement operations on 25 patients. Sodium nitroprusside (Nipride, Roche), in the form of a 0.01 per cent (100 µg/ml) infusion, was used as a hypotensive agent. The mean arterial blood pressure (MABP) was lowered from 108 to 64 mmHg (range 60–70) ($P < 0.001$). The average blood loss during the operations was 212 ml and none of the patients required homologous blood transfusion. In comparison with 25 normotensive patients undergoing similar surgery, the difference in the mean volume of haemorrhage between the two groups was 826 ml ($P < 0.001$). The difference in the total haemorrhage, however, between the same two groups was 518 ml (mean) ($P < 0.01$). The results were compared with those of another investigation in which epidural anaesthesia was used to diminish bleeding during surgery on the hip.

Key words: controlled hypotension; sodium nitroprusside; transfusion during surgery

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Induced hypotension in major surgical operations has been in vogue for several years yet its application has been hampered by occasional unpleasant side effects caused by either a lack of knowledge of the hypotensive agent or of the technique used to accomplish the diminished bleeding. The earlier hypotensive techniques of arteriotomy (Bilsland 1951) were abandoned in favour of more beneficial methods when the autonomic ganglion blocking agents were introduced, providing a relatively avascular field for surgical procedures (Royester et al. 1951, Steven & Tovell 1954, Holms 1956, Nayman 1960). Deliberate hypotension has been employed in thoracic surgery (Lewis 1951), prostatic surgery (Bruce 1960) and in large blood vessel surgery (Glenn et al. 1954) in

order to diminish the blood loss. It has also been used to attain ischaemia of the surgical wound in orthopaedic surgery (Holms 1956), in gynaecological surgery (Linacre 1961) and in reconstructive plastic surgery (Enderby 1961). Deviations from the normal clinical state, such as hypovolaemic anaemia and polycythaemia, have been clear-cut contraindications in the same way as cardiovascular or cerebrovascular, renal or hepatic pathological involvement. In spite of the fact that there has been considerable criticism of hypotensive anaesthesia, the promising results after surgical ischaemia cannot be denied (Gillies 1950, Safar 1955, Enderby 1961, Learmonth 1976). Nevertheless, deliberate hypotension cannot be regarded as a routine procedure and it is

employed only when specifically indicated (Eckenhoff 1955, Adams 1975). After the initial introduction of methonium compounds in induced hypotension, trimetaphan (arfonad) became very popular due to its evanescent action (Nicholson et al. 1953). Later clinical experience, however, showed that its application was not all that straightforward (Payne 1956) because of the histamine release. Moreover, it often created problems due to tachyphylaxis. Halothane has been used as an adjuvant to hypotensive drugs (Smith et al. 1960, Neill & Nixon 1965, Taylor et al. 1970) but its application in elderly people cannot be entirely justified as it has a potent myocardial depressive action. The introduction of sodium nitroprusside (SNP) has eliminated many of the hazards of ganglion blocking agents although its administration by experienced anaesthesiologists is absolutely essential due to its highly potent action. Its use has been declared safe by Vesey et al. (1976) (with appropriate authenticity) provided the dose does not exceed a maximum of 1.5 mg/kg body wt. This investigation was conducted to assess the volume of haemorrhage during as well as after surgery on the hip using SNP in the dose recommended by the above-mentioned authors (Vesey et al. 1976).

PATIENTS AND METHODS

A comparative study was conducted of 50 patients with coxarthrosis who were operated on and fitted with a Charnley prosthesis. The patients com-

prising this group showed no signs of cardiovascular or other systemic diseases. (Deliberate hypotension has been employed in just over 300 orthopaedic patients and the same clinical criteria have been observed in each case.) The standard Charnley operative technique was used. Postoperatively the patients were treated routinely with Warfarin sodium (marevan). Twenty-five patients were operated upon under normotension (NTN) and in the remaining 25 patients controlled hypotension (CHN) was induced prior to operation. There were nine patients who were operated on bilaterally, i.e. on one side under NTN and on the other side under CHN. The average age of the patients, 36 women and 14 men, in both the groups was 70.4 years. The ranges, however, varied slightly, being 57–86 years in the normotensive group and 55–80 years in the hypotensive group (Table 1).

The surgical haemorrhage was measured by weighing the wet swabs and the towels. Postoperative blood loss was determined by measuring the volume of blood in the vacuum drain, which was usually removed 1–3 days after the operation. A meticulous watch was kept on the postoperative diuresis and a comparison was made with the normotensive group. At the time of insertion of the acrylic material, the clinical changes in the patient, if any, were closely observed. The patients were not given prophylactic treatment with antibiotics or hydrocortisone.

The number of blood transfusions was determined and compared with the normotensive group. In the event of blood loss exceeding 500 ml, homologous blood was used for replacement. The hypotensive group included a patient who refused blood transfusion on religious grounds and her wishes were complied with. Her haemoglobin level dropped from 13.6 g on the day of operation to 11.4 on the following day. It returned to normal during the subsequent days.

The results of this investigation were compared with a study conducted at the Academic Hospital,

Table 1. Patients treated for coxarthrosis with Charnley's prosthesis under normotension (NTN) or controlled hypotension (CHN) and light balanced anaesthesia. (Data given as mean and range.)

No. of patients	Normotension 25	Controlled hypotension 25
Age (years)	70.4 (57–86)	70.4 (55–80)
Weight (kg)	68.6 (52–85)	69 (54–90)
Hb (g%)	13.8 (11.7–16.8)	13.9 (12.2–16.9)
Duration of operation (min)	109.4 (95–120)	94 (82–105)

Uppsala, Sweden (Jakobson & Wigren 1972). The 21 patients in this study underwent 27 operations using Muller's prosthesis on the hip. Twelve patients in this group received epidural anaesthesia and 15 were operated under general anaesthesia.

ANAESTHETIC TECHNIQUE

After a standard premedication with atropine 0.6 mg, pethidine 50–100 mg and promethazine 25–50 mg (Hopkins et al. 1957) 1 hour before the operation, anaesthesia was induced using methohexitone 70–100 mg, followed by suxamethonium 50 mg. All the patients were artificially ventilated (IPPV & Hyperventilation) with a mixture of 50–50 per cent oxygen and nitrous oxide. Analgesia was provided using fentanyl and further muscular relaxation was obtained with d-tubocurarine (Albertson et al. 1956, Neill & Nixon 1965). All the patients received 1.0 l Ringer's acetate and 1.0 l fructose on the day of the surgery.

Prior to the commencement of sodium nitroprusside infusion (0.01 per cent solution in 5.5 per cent glucose), an intra-arterial cannula was

inserted into the radial artery for the continuous monitoring of the mean arterial blood pressure (MABP). Five minutes before the skin incision the MABP was lowered to 60–65 mmHg Torr and this was maintained throughout the surgery. Halothane was added only when absolutely necessary. The SNP infusion was discontinued just before the closure of the surgical wound in order to restore the blood pressure to the pre-SNP levels. The surgeon was then asked to check the bleeding points if any. The recording of the MABP was as in Table 2. Arterial blood specimens were collected before, during and after the administration of SNP, in order to keep an eye on any possible changes in the blood chemistry of the patient. All the patients were lying in the supine position during surgery.

RESULTS

Haemorrhage during surgery. The average blood loss during controlled hypotension was 212 ml (range 160–350 ml). In the normotensive group the mean surgical

Table 2. Mean arterial blood pressure (MABP) in mmHg (range in parentheses)

Normotension		Controlled hypotension	
At admission	126.1 (87–180) ^a	At admission	125.2 (85–183)
Before induction of anaesthesia	114 (80–107) ^b	Before induction of anaesthesia	108.2 (90–130) ^c
During operation	93.7 (80–107)	After induction of anaesthesia	91.8 (73–117) ^d
		During SNP infusion	64.4 (60–70) ^e
		10 mins after discontinuation of SNP	92.6 (78–120)
After extubation	98.8 (75–133)	After extubation	104.1 (85–127)
At recovery from anaesthesia	116.2 (80–140)	At recovery from anaesthesia	119 (83–143)

Difference a–b=20.3 (N.S.)

Difference c–d=16.4 ($P<0.05$)

Difference c–e=43.8 ($P<0.001$)

Table 3. Mean haemorrhage in ml (range in parentheses)

	Normotension	Controlled hypotension
Haemorrhage during operation	1038 (500–1750) ^a	212 (160–350) ^b
Postoperative haemorrhage	808 (590–1205)	877 (695–1130)
Total haemorrhage	1846 (1090–2725) ^c	1328 (905–1335) ^d

Difference a–b=826 ($P<0.001$)

Difference c–d=518 ($P<0.01$)

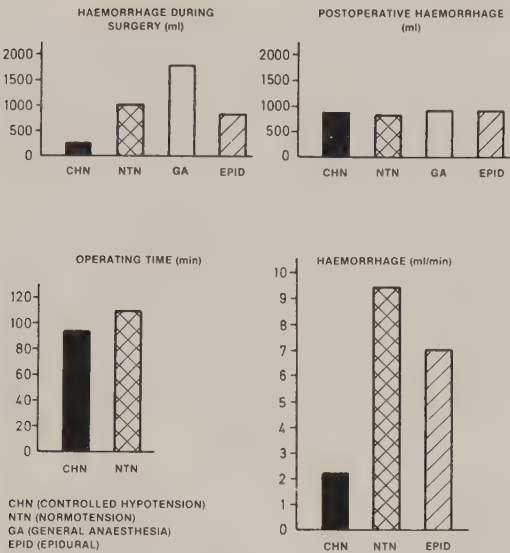


Figure 1. Haemorrhage and operating time during surgery for total hip replacement with different anaesthetic techniques

haemorrhage was 1038 (range 500–1750 ml). The difference between the two groups was highly significant, i.e. 826 ml ($P<0.001$) (Table 3). In the Swedish investigation, the average blood loss was 1775 ml using general anaesthesia but it was reduced to 820 ml using epidural anaesthesia (Figure 1). The difference between the epidural and the hypotensive groups was also highly significant ($P<0.001$).

Postoperative haemorrhage. It was noted that the blood loss after CHN was slightly more (mean 877, range 695–1130 ml) as compared with NTN (mean 808, range 590–1205 ml). The difference, however, was clinically insignificant (Table 3). In the work done at Uppsala the postoperative blood loss was 900 ml with both epidural and general anaesthesia (Figure 1).

Total haemorrhage. The total blood loss under controlled hypotension was on average 1328 ml (range 905–1335 ml) as compared with the normotensive group where the mean haemorrhage was 1846 ml (range 1090–2725).

The difference between the two groups was significant ($P<0.01$) (Table 3).

Operating time. The operating time was reduced to a certain extent, i.e. from a mean of 109.4 min (range 95–120) with normotension to a mean of 94 min (range 82–105) with hypotension ($P<0.05$) (Table 1).

Bilateral total hip replacement. In the nine bilaterally operated patients the difference in the blood loss during the operations was on average 820 ml. The operating time was reduced by 15 per cent.

Blood transfusions. A blood loss of more than 500 ml was replaced by homologous blood during the operation or immediately afterwards. With CHN the patients required an average of 1.6 units of blood. Under NTN the unilateral and the bilateral hip replacements needed 3.3 and 3.16 units of blood, respectively. Under hypotension not a single patient required transfusion during surgery. The difference in blood transfusions between the normotensive and hypotensive groups was highly significant ($P<0.001$).

Clinical evaluation of the patients

The following unusual complications were observed,

	Normotension	Controlled hypotension
Moderate haematoma	1	—
Thrombophlebitis	2	1
Myocardial insufficiency (moderate, total haemorrhage 2725 ml)	1	—
Supraventricular tachycardia during SNP infusion (treated with practolol)	—	1
Moderate reduction in P_{O_2}	—	6
Accidental fracture	—	1

Under SNP-induced hypotension one patient developed a tachycardia of 150/min. She was treated with practolol and the pulse stabilized and no further complications ensued. One patient needed 0.5–1 per cent halothane in order to maintain the MABP at the desired low level. During SNP administration there was an arterial reduction of P_{O_2} in six patients (mean reduction 13.2 per cent) as compared with pre-SNP levels. However all patients acquired their normal P_{O_2} levels after the discontinuation of sodium nitroprusside. Postoperatively, there was one incident of thrombophlebitis in the hypotensive group 30 days after surgery. It was not related to SNP and the patient was treated successfully. A moderate haematoma occurred in the normotensive group. There were no such complications after SNP administration. One of the hypotensive patients sustained a fracture of the femur, on the day before discharge. She was reoperated upon and had to stay in the hospital for several months. This patient had been doing very well before this accident happened and it could not be attributed in any way to the hypotension. The postoperative diuresis was delayed in patients in the hypotensive group but when compared to the normotensive group there was no significant difference clinically. There was no incidence of oliguria or anuria in patients given controlled hypotension. At the time of the insertion of the acrylic material there was no change in any of the parameters being monitored continuously. However, there was a slight reduction in systolic blood pressure in two of the normotensive patients (a mean reduction of 11 per cent). The postoperative clinical evaluation was conducted with the assistance of the medical department of the clinic. In the 25 patients investigated, there was no evidence of cardiovascular, cerebrovascular, renal or hepatic complications immediately after surgery or during the ensuing days. All the patients were discharged after an average hospital stay of 31 days (range 29–41) with the exception of the patient who sustained a fracture of the femur.

DISCUSSION

Systematic hypotension without compensatory oxygenation of the central nervous system leads to neuropathological consequences derogatory to cerebral function due to reduction in the cerebral blood flow. However, the circulatory insufficiency responsible for the diffuse changes in the brain of the Rhesus monkey, in the study by Brierley & Excell (1966), has not been attributed entirely to the systemic hypotension but to a combination of hypotension and the head-up position of the subject (Adam et al. 1966). This combination results in a markedly reduced oxygenation of the brain tissue and thus a deleterious effect on brain metabolism (Brierley & Excell 1966). The effects of deliberate hypotension on cerebral haemodynamics are dependent largely on the compensatory mechanisms present in an individual. There appears to be little danger of cerebral anoxia in the supine position when the mean arterial blood pressure is reduced to a level as low as 55 mmHg (Morris et al. 1953) with ganglion blockade. There is no evidence of cerebral dysfunction in induced hypotension as long as the blood flow in the brain is not interrupted significantly (Slack & Walter 1963). Deliberate hypotension is regarded as safe, as long as the systolic blood pressure is not reduced below 50 mmHg (Slack & Walter 1964). In actual practice, levels of mean arterial blood pressure lower than 60–65 mmHg are not necessary and no undesirable effects have been reported with a combination of careful monitoring and correct positioning of the patient subjected to induced hypotension (Royester et al. 1951, Eckenhoff 1955, Tough 1960, Enderby 1961, Linacre 1961, Lindop 1975). Continuous arterial monitoring is a simple procedure and without ill-effects on the patients (Brown et al. 1969, Zorab 1969). This was achieved in all 25 patients in the present investigation and did not inconvenience the patients in any way. There were no psychological disturbances, assessed on the same principles as suggested by Eckenhoff et al. (1964).

Respiratory function has not been found to be reduced after exposure to deliberate hypotensive anaesthesia. On the contrary it has been proposed that hypotension can increase the vital capacity of the patient (Bromage 1956). There was no evidence of any significant changes in the pattern of diuresis as compared to normotensive anaesthesia. Measurement of diuresis in relatively short-term surgery (mean operating time, 94 min) was considered unjustifiable due to the possible risk of infection. Previous studies have shown that induced hypotension does not significantly change the renal blood flow, due to the presence of compensatory mechanisms resulting in renal vasodilatation and increased renal plasma flow offering protection from significant anoxic effects (Shipley & Study 1951, Miles et al. 1952, Evans & Enderby 1952).

After these comprehensive studies on the capability of the vascular system to withstand a low systolic blood pressure of 50 mmHg and attain recovery by compensatory methods (Kohlstaedt & Page 1943), patients were submitted to a brief period of simulated shock, with simultaneous continuous monitoring, with beneficial results. In addition to trials with arteriotomy (Bilsland 1951), high spinal anaesthesia has been employed concomitantly to facilitate surgery (Sarnoff & Arrowood 1946, Lynn et al. 1952). Thus surgery on the hip which was considered a serious undertaking has been rendered more beneficial and without grave after effects (Kern 1952, Welch et al. 1975, Donaldson 1975). Nevertheless the fact remains that, in the performance of arthroplasty, both trauma and profuse haemorrhage remain a challenge to the surgeon and the anaesthesiologist. The prevention of shock can be accomplished by efficient surgical techniques and prompt blood

transfusion (Keith 1977) but it is a disturbing fact that one has to submit these often old and frail patients to massive blood transfusions.

For several years methonium compounds as well as trimetaphan (arfonad) have been employed to avoid cumbersome blood transfusions or in the majority of the cases diminish them. Recent clinical application of a peripheral vasodilator, sodium nitroprusside, which was recommended as early as 1929 by Johnson, has solved many problems for those engaged in hypotensive anaesthesia. However, its high potency and the use of inadvertently large doses have led, in a few cases, to highly disappointing results (MacRae & Owen 1974 and others) which cannot be overlooked. After its initial clinical trials (Page et al. 1955, Moraca et al. 1962, Taylor et al. 1970, Siegal et al. 1971), its metabolic effects have been extensively investigated (Vesey et al. 1974, 1976) and it has been found not to cause any significant changes in cerebral haemodynamics (Griffiths et al. 1974). It is thus considered superior to other hypotensive agents (Styles et al. 1973, Landauer 1976). It can, however, cause tachycardia as well as moderate reduction in the arterial PO_2 levels, but these return to normal levels after its discontinuation (Wildsmith et al. 1975). The maximum dose which earlier was considered to be 3.5 mg/kg body wt. (McDowall et al. 1974) has been reduced to 1.5 mg/kg body wt. after comprehensive investigations (Vesey et al. 1976). In the study reported herein an average dose of 0.54 mg/kg body wt. was employed (Table 4), which is well below the recommended maximum dose. In a further investigation it has been demonstrated that the dosage of SNP can be successfully lowered by using larger doses of neuroleptic drugs in patients undergoing a variety of different types of surgery (Vazeery et

Table 4. Sodium nitroprusside (SNP) infusion

Duration of SNP infusion (mean and range)	80 (66–100) min
Amount of SNP (mean and range)	37.4 (13–50) mg

al.). Its use over longer periods is not recommended (Nourok et al. 1964). Controlled hypotension accomplished by a combination of sodium nitroprusside, curare (Thomas 1957, Neill & Nixon 1965), and moderate hyperventilation (Schieve & Wilson 1953, Harp & Wollman 1973) can be extremely beneficial to a patient undergoing total replacement of the hip, provided the clinical state of the patient is monitored continuously by experienced anaesthesiologists. It has its value in major orthopaedic surgery when it is mandatory to avoid large blood transfusions.

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Correspondence to: Afzal K. Vazeery, Department of Anaesthesiology, Central Hospital of Rogaland, Stavanger, Norway.

DELIBERATE ARTERIAL HYPOTENSION IN PLASTIC SURGERY FOR THE REDUCTION OF HYPERTROPHIC BREAST

*A Critical Appraisal of Surgical Ischaemia and Haemodynamic Changes
during Sodium Nitroprusside Infusion*

Afzal K. Vazeery, Kristin Aspelund and Ingemar Ahlgren

*From the Departments of Anaesthesiology (Heads: T. Ursfjord and A. K. Vazeery) and Plastic Surgery
(Head: I. Dommersnes), Central Hospital of Rogaland, Stavanger, Norway,
and the Department of Anaesthesiology (Heads: O. Lundskog and I. Ahlgren),
Malmö General Hospital, Malmö, Sweden*

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Abstract. Deliberate hypotension was used to attain surgical haemostasis in thirteen patients undergoing plastic and reconstructive surgery on breast, with an 0.01% sodium nitroprusside (SNP) infusion and concomitant deep neuroleptanaesthesia. The mean surgical haemorrhage was 217 ml in the hypotensive group and when compared with a group of 13 normotensive patients, in whom the average blood loss was 688 ml, the difference was highly significant. A continuous monitoring of the changes in the circulatory dynamics, by electrical impedance plethysmography which was sustained before, during and after the application of SNP, revealed considerable enhancement in the cardiac output as well as the peripheral blood flow of all patients investigated. There was a moderate increase in the stroke volume of a majority of patients. The total systemic resistance was greatly diminished in all the patients submitted to hypotensive anaesthesia with nitroprusside. The clinical criteria were also compared with another group of fourteen patients where arfonad (trimetaphan) was employed to induce hypotension. The difference in bleeding between the two hypotensive groups was insignificant. Neither sodium nitroprusside nor arfonad induced hypotension necessitated any blood transfusion, during or after the surgery.

The accomplishment of profound ischaemia by induced hypotension, in manifold surgical procedures, has become a reality at many medical centres engaged in intricate forms of major surgery. This implies particularly to the field of reconstructive plastic surgery, where it is manipulated in the context of a beneficial aid, in attaining admirable results without being cumbersome to the patient, whose safety is obviously a matter of prime importance. Despite the fact that several clinicians have

endeavoured to achieve this goal, one tends to concede that it has been done so, occasionally with a certain physiological inconvenience caused to the patient, though inadvertently. The recent advances in the monitoring techniques during anaesthesia in the presence of adequate artificial ventilation, not only assist in maintaining a vigilant watch on the clinical state of the patient, but also facilitate the joint effort, on the part of both the surgeon and the anaesthesiologist, in improving their respective skills. After initial investigations to induce hypotension by spinal anaesthesia (Green, 1952) and the ganglion blocking agents such as hexamethonium (Evans & Enderby, 1952; Haynes, Morris, Moyer & Snyder, 1953; Cox, 1953) arfonad has enjoyed being the agent of first choice, in procuring profound haemostasis in surgery (Anderson, 1955; Clark, Bennet & Flaatt, 1955; Converse & Boba, 1957; Bichley & Kittle, 1962; Feikes, Syphers & Hinshaw, 1962; Hopkins, Friatiannne, Penn, Sagba & Simeone, 1964; Hopkins & Simeone, 1964), either alone or in combination with halothane. However, deep halothane anaesthesia alone has proved fruitful in acquiring exsanguinous operating fields (Hugosson & Högström, 1973). The implications of deliberate hypotension, with regard to its benefits as well as drawbacks, have been elaborately scrutinised (Eckenhoff, 1955; Chamberlain, Mannheimer & Keats, 1963; Bodman, 1964; Eckenhoff, Neil, Shanks & Leigh, 1974; Reves, Shepard, Wallach & Lell, 1978). The clinical evaluation of sodium nitroprusside as a vasodilator agent

Table I. Patients treated for bilateral hypertrophy of the breast under normotension and controlled hypotension with arfonad or sodium nitroprusside (SNP) with concurrent deep neuroleptanaesthesia

Data given as mean and range

No. of patients. . .	Normotension 13	Arfonad hypotension 14	SNP hypotension 13
Age (years)	40 (20–57)	38.8 (22–52)	35 (19–61)
Weight (kg)	68 (50–77)	66.6 (52–75)	61 (49–74)
Hb (g %)	13.7 (12–15.4)	13.7 (12.5–14.6)	13.5 (12.5–14.5)
Hct (pvc %)	40.3 (37–48)	39.8 (37–43)	41.4 (38–46)
Duration of operation (min)	115 (108–135)	99 (96–112)	97 (94–108)

(Page, Corcoran, Dustan & Koppanyi, 1955; Schlant, Tsagaris & Robertson, 1962), subsequently encouraged its trials in controlled hypotension (Taylor, Styles & Lemming, 1970). Its pharmacological merits and demerits have been extensively studied in the ensuing years. It is considered to be of immense value, not only in hypertensive crisis (Wilbrandt, Piehl, Neuhaus, Freyland, Freund, Gohring, Behrenbeck & Fritz, 1970; Palmer & Lasseter, 1975) but also, it is rapidly gaining predominance now, in hypotensive anaesthesia (Stoyka & Schutz, 1975; Vesey, Cole & Simpson, 1976) provided its employment is accompanied by a continuous and careful monitoring of the patient under treatment. However, its use has been reported mostly in combination with halothane which itself is a cardio-circulatory depressant.

The purpose of this study was to investigate the effect of hypotensive anaesthesia in minimal doses, on the surgical haemorrhage as well as haemodynamics, in patients receiving deep neuroleptanaesthesia.

MATERIAL AND METHODS

Forty women with enlargement of their breasts were investigated. 13 patients were operated under normotension, 14 were submitted to induced hypotension with trimetaphan while in the remaining 13 patients controlled arterial hypotension was accomplished by sodium nitroprusside infusion.

The average age of the patients in the three groups was 40, 38.8 and 35 years, respectively.

Prior to the surgery an appropriate clinical screening was conducted in order to exclude any cerebrovascular, cardiocirculatory or systemic disease. An examination of both haemoglobin and haematocrit was conducted before as well as immediately after the surgery (Table I).

The nature of the surgical procedure and the hypoten-

sive technique was explained to all the patients and their consent obtained. The blood loss during the surgery was measured by weighing the wet swabs and the towels while postoperatively, the haemorrhage was determined from the vacuum drain which was removed 3–5 days after the operation. A vigilant watch was maintained on all the patients, at the recovery department with regard to any untoward behaviour, cardiocirculatory insult or any probable disturbance in the pattern of diuresis. The patients did not receive any prophylactic treatment with antibiotics. The circulatory dynamics, before, during and after the SNP infusion, was continuously monitored by a non-invasive technique of electrical impedance plethysmography (Minnesota impedance cardiograph) which has been described by Bache, Harley & Greenfield, 1969; and Kubicek, Patterson & Witsoe, 1970. This method has been further elaborated by other investigators (Hill & Low, 1973). The mean arterial pressure (MAP) as well as the central venous pressure (CVP) were incessantly recorded by a disposable Pressurveil transfer unit with membrane depressor tube connected directly to the respective pressure gauge (CONCEPT Inc, USA). During arfonad infusion, the minute-to minute recording of the MAP was rendered by the Instrument electronic sphygmomanometer (Cardy 8 mini, Japan).

Anaesthetic technique

All the patients received a premedication with atropine 0.5 mg, pethidine 75–100 mg and promethazine 25–50 mg, 1 hour prior to the surgery. Induction of anaesthesia was made with fentanyl 0.4–0.5 mg and droperidol 5 mg. Patients were put to sleep with injection of methohexitone 70–100 mg and muscle relaxation was attained by *d*-tubocurarine chloride. Further analgesia was accomplished by larger supplementary doses of neuroleptic drugs combined with muscle relaxation. During controlled hypotension halothane was used as an adjuvant when needed.

During hypotensive anaesthesia the infusion of the hypotensive agent was discontinued before the closure of surgical wound and the mean arterial pressure allowed to rise, thus facilitating a satisfactory control over haemostasis. All the patients received 1.0 l of ringer acetate and 1.5 l of fructose on the day of operation. The blood loss was replaced by homologous blood when it exceeded 0.5 l.

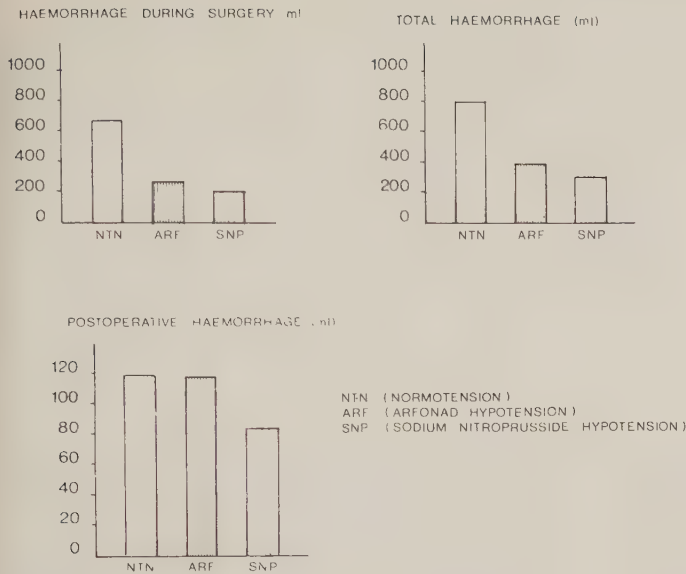


Fig. 1. Haemorrhage during surgery under normotension, arfonad and SNP infusions.

The patients lay supine and were moderately hyperventilated with 50–50% oxygen and nitrous oxide gas mixture.

RESULTS

The average blood loss during normotension was 688 ml (range 210–1320). During controlled hypotension with arfonad it had an average of 281 ml (range 185–470) while the SNP hypotensive group showed a mean haemorrhage of 217 ml (range 120–380) (Fig. 1). The difference between normotension and the induced hypotension was highly significant ($P < 0.001$). The difference in bleeding between the two hypotensive groups, however, was comparatively less significant ($P \approx 0.05$) (Table II).

It was observed that there was no significant difference in the postoperative haemorrhage between the normotension and arfonad hypotension. On comparing normotension and SNP hypotension the difference in the postoperative bleeding, however, was significant ($P \approx 0.075$). The difference in the total haemorrhage between normotension and controlled hypotension (both arfonad and SNP-induced) was highly significant ($P < 0.001$) (Table II) (Fig. 1).

A surgical haemorrhage of more than 0.5 l was replaced by homologous blood during the surgery or in the immediate postoperative period. The patients received an average of 0.86 units of blood during normotension. None of the patients in the

Table II. Mean haemorrhage in ml and weight of resected fat tissue in g (range in parentheses)

	Normotension	Arfonad hypotension	SNP hypotension
Haemorrhage during operation	688 (210–1320) ^a	281 (185–470) ^b	217 (120–380) ^c
Postoperative haemorrhage	118 (35–330) ^d	116 (40–210)	85 (30–120) ^e
Total haemorrhage	806 (354–1650) ^f	397 (230–550) ^g	302 (235–405) ^h
Weight of fat tissue removed			
Left breast	569 (390–800)	558 (380–800)	550 (400–790)
Right breast	549 (390–800)	546 (380–810)	562 (395–815)

Difference $a-b$, $c=407$, 471 ($P < 0.001$).

Difference $b-c=64$ ($P \approx 0.05$).

Difference $d-e=33$ ($P \approx 0.075$).

Difference $f-g$, $h=409$, 504 ($P < 0.001$)

Table III. Mean arterial pressure (MAP) in mmHg (range in parentheses)

	Normotension	Controlled hypotension	
		Arfonad	SNP
Before induction of anaesthesia	99.9 (80–122) ^a	98.8 (90–110) ^c	98.3 (90–114) ^e
During operation	92.2 (81–108) ^b	63.2 (60–70) ^d	62.5 (60–65) ^f
After recovery from anaesthesia	95.0 (89–112)	89.0 (80–95) ^g	97.4 (90–108)
Difference $a-b=7.7$ =(NS)			
Difference $c-d=35.6$ =($P<0.001$).			
Difference $e-f=35.8$ =($P<0.001$).			
Difference $c-g=9.8$ =($P<0.05$).			

hypotensive group required blood transfusion. The difference between the two groups, in this aspect, was very significant ($P<0.001$). The fall in the mean arterial pressure in both arfonad as well as SNP hypotension was most significant as compared to the preoperative levels ($P<0.001$) (Table III).

At the termination of surgery, the restoration of mean arterial pressure to the pre-anaesthetic levels, was not always easy during arfonad-induced hypotension. In 7 out of 14 cases, a plasma volume expander (dextran) was employed and it proved helpful in 5 patients in restoring the blood pressure. However, in 2 patients it was of little avail and a pressor agent such as ephedrine was resorted to. The postoperative levels of MAP, however, remained lower as compared to the pre-arfonad levels ($P<0.05$). Such observation was rarely encountered after discontinuation of SNP infusion (Table III). Supplementary halothane was required in 10

out of 14 patients in order to accomplish the desired low levels of MAP. No halothane was needed during nitroprusside infusion.

During SNP infusion there was a considerable fall in the mean central venous pressure as well as the peripheral vascular resistance (Fig. 2). The difference when compared to the preoperative levels was highly significant ($P<0.001$). Their values, however, rose rapidly in the recovery phase (Table IV). The heart rate during the treatment with nitroprusside, was augmented significantly thereby affecting the cardiac output which became considerably enhanced ($P<0.01$). In addition to the increase in heart rate there was a moderate increment in the left ventricular stroke volume ($P\approx 0.05$) (Table IV) (Fig. 2). The increase in the stroke volume persisted even after the discontinuation of SNP and remarkably enough, maintained a fairly stable cardiac output by compensating for the reduced heart

Table IV. Haemodynamic parameters before, during and after SNP infusion with concomitant deep neuroleptanaesthesia in 13 women

	I Before (mean $\pm$ S.E.M.)	II During (mean $\pm$ S.E.M.)	III After (mean $\pm$ S.E.M.)					
Mean arterial pressure (mmHg)	98.3 $\pm$ 3.0	62.5 $\pm$ 0.6	97.4 $\pm$ 1.2					
Central venous pressure (cmH ₂ O)	7.1 $\pm$ 0.3	2.3 $\pm$ 0.3	5.9 $\pm$ 0.3					
Stroke volume (ml)	66.4 $\pm$ 2.2	70.3 $\pm$ 2.4	74.5 $\pm$ 2.6					
Heart rate (beats/min)	83 $\pm$ 2.5	105 $\pm$ 3.9	77 $\pm$ 1.4					
Cardiac output (L/min)	5.5 $\pm$ 0.1	7.2 $\pm$ 0.1	5.9 $\pm$ 0.3					
Peripheral vascular resistance dynes/sec/cm ⁻⁵)	1 419 $\pm$ 43	694 $\pm$ 19	1 343 $\pm$ 43					
Limb blood flow (ml/min)	133 $\pm$ 7.0	204 $\pm$ 12	164 $\pm$ 8					
Hematocrit (pcv %)	41.4 $\pm$ 0.7	—	37.3 $\pm$ 0.4					
	MAP	CVP	SV	HR	CO	PVR	LBF	HCT
Difference I-II=	**	***	*	**	**	***	***	—
Difference I-III=	0	*	*	*	*	0	*	*
* = p $\leq$ 0.05; ** = P $<$ 0.01; *** = p $<$ 0.001; 0 = N.S.								

*= $p\approx 0.05$; **= $P<0.01$; ***= $p<0.001$; 0=N.S.

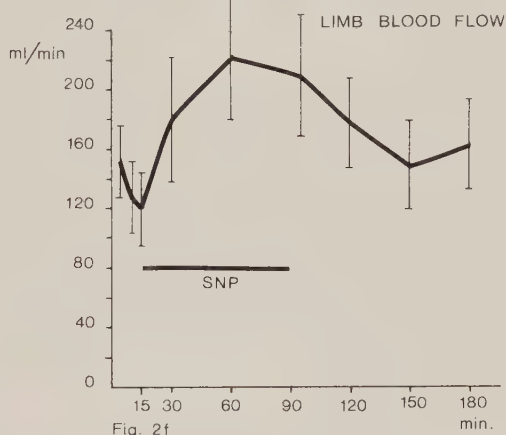
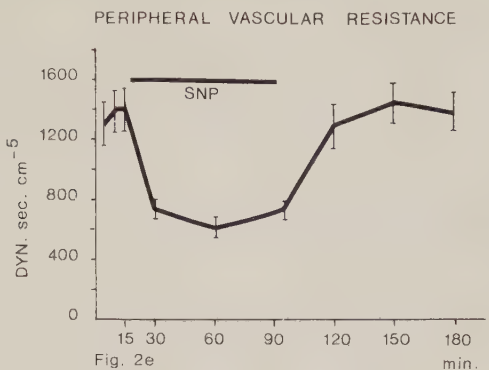
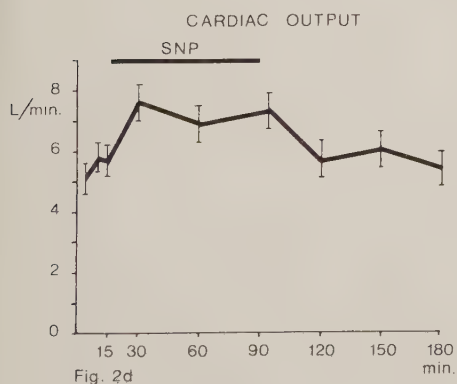
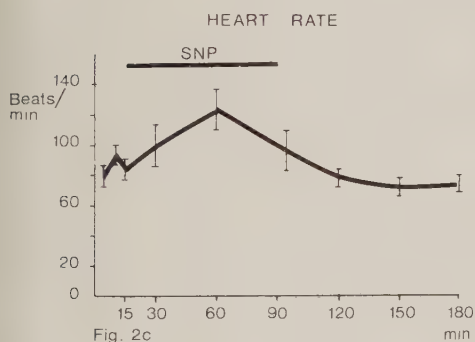
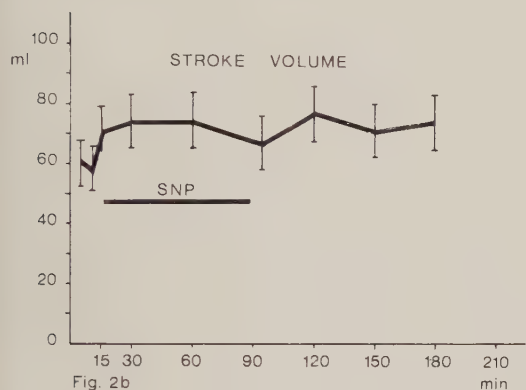
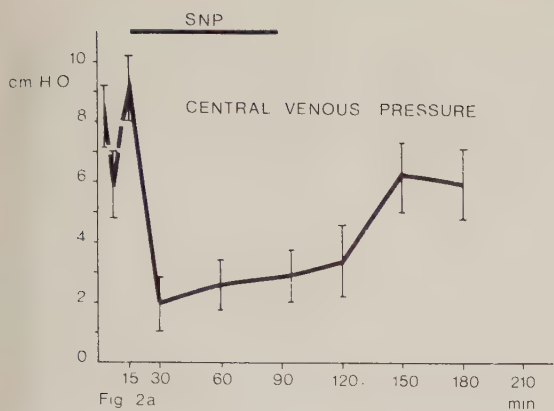


Fig. 2. Haemodynamic parameters before, during and after SNP infusion with concomitant deep neuroleptanaesthesia in 13 women, operated for the reduction of hypertrophic breast.

rate, in the postoperative phase (Table IV). The increase in blood flow in the limb, during induced hypotension with nitroprusside was again highly significant ($P < 0.001$), and there was manifest higher peripheral blood flow in the immediate postoperative period (Fig. 2).

There was no evidence of reactionary haemorrhage or haematoma in the group of patients investigated. After arfonad induced hypotension the recovery from anaesthesia was delayed in a majority of women (due to supplementary halothane) and in two patients a slight difficulty in vision persisted for several hours after the surgery. These patients had fairly dilated pupils and were implied to have acquired it after larger doses of arfonad. Three patients responded poorly to trimetaphan and adjuvant deep halothane anaesthesia was resorted to.

The blood-gas analysis which was conducted before, during and after the application of hypotensive

Table V. *Postoperative complications*

	Normo-tension	Arfonad hypo-tension	SNP hypo-tension
Delayed recovery	1	10	1
Disturbance of vision	0	2	0
Reduction in P_{O_2}	—	0	2
Plasma volume expanders (dextran)	1	7	0
Pressor agents (ephedrine)	0	2	0
Tachyphylaxis	—	3	0

agents, showed a mean reduction in P_{O_2} of 13.5% in 2 patients, only during SNP infusion. These values, however, returned to preoperative levels at the recovery. The pattern of diuresis did not vary specifically in the 3 groups studied, though delayed diuresis was occasionally noticed in all three groups of patients. The medical as well as the nursing personnel, did not observe any abnormal behaviour amongst the patients who were subjected to deliberate arterial hypotension, throughout their stay at the hospital (Table V).

The minimal doses employed during SNP infusion could envisage desirable hypotension without any physiological setback to the patient (Table VI).

DISCUSSION

During a state of inadequate tissue perfusion the availability of excessive quantities of oxygen both at ambient as well as higher pressures is of doubtful value. In an investigation on haemorrhagic shock such doubts have been invariably confirmed (Cain & Connolly, 1967). During cerebral ischaemia induced by acute arterial hypotension, although there is a profound variation in the low levels of mean arterial blood pressure causing this ischaemia, there is no appreciable difference in the value for the cerebral blood flow procuring such a complication (Finnerty, Witkin & Fazekas, 1954). Thus it is quite obvious that any process, that tends to undermine an adequate blood flow and the tissue perfusion in the central nervous system, will eventually incur irreversible damage no matter how efficient the methods, that were being instituted to restore the deterioration in the affected tissues. Deliberate hypotension is a state simulating shock but without

Table VI. *Sodium nitroprusside (SNP) infusion (mean and range)*

Duration of SNP infusion, min	75 (62–98)
Amount of SNP, mg	34.5 (16–60)

the hazards of hypovolaemia, diminished perfusion or undermined cerebral blood flow. The sensitivity of brain to acute hypotension, as a consequence of cerebral insufficiency without simultaneous clinical or laboratory evidence of coronary insufficiency has been documented (Finnerty et al.). The selection of hypotensive agents such as trimetaphan in clinical practice (Smith, Didier & Clagett, 1960; Hopkins et al.) with adjuvant halothane facilitates the accomplishment of tissue ischaemia and its merits not to cause anaerobic metabolism are highly appraisable.

The drawbacks of trimetaphan such as tachyphylaxis and temporary disturbances of vision postoperatively, can be remedied by curtailing its dosage and supplementing it with halothane which of course may consequently delay the recovery from anaesthesia.

Hypotensive agents such as trimetaphan and sodium nitroprusside which are capable of reducing systemic vascular resistance, improve cardiac performance by dint of their vasodilator action although previously, trimetaphan has been acclaimed to do so, solely due to its positive inotropic action on the myocardium (Chatterjee & Parmley, 1977; Nitter-Hauge, 1978).

Halothane has often been accredited for its potential protective capability against the pernicious effects of low perfusion pressures in the tissues. Deep halothane concentrations which often became mandatory, during arfonad infusion, in the investigation conducted herewith, do not tend to cause appreciable metabolic acidosis in experimental animals (Nilsson & Siesjö, 1971) unless associated simultaneously with marked hyperventilation and profound hypotension, where the mean arterial pressure is lowered to 30–40 mmHg. However, there is evidence of diminished coronary blood flow during deep halothane anaesthesia along the other well known depressed physiological parameters, such as cardiac output, pulse rate and left ventricular work in an experimental study made in normovolaemic dog (Ahlgren, Aronsen, Björkman & Wetterlin, 1978), although no detrimental effects were ob-

served in pulmonary, cerebral and hepatic circulation. Sodium nitroprusside, despite having several positive inotropic actions of the cardiocirculatory system, has been considerably criticised, due to its high potency and the ill-effects ensuing from its uncontrolled application. The valuable research papers, published on the fate of its metabolism by Vesey, Cole, Linnell & Wilson (1974) and Spiegel & Kucera (1977) warrant its administration under meticulous care and in restricted doses, both during the treatment of hypertensive crises as well as in the management of controlled arterial hypotension. Its application in minimal pharmacological doses, when observed as a prerequisite, seems to guarantee pronounced cardiovascular stability, although the temporary side effects such as impending tachycardia and occasional moderate reductions in the arterial oxygen tension, may justify due concern. The work reported in this paper confirms the work of other authors in certain aspects while it differs in some vital criteria, namely the left ventricular stroke volume, both during as well as after sodium nitroprusside infusion with concomitant deep neurolept-anaesthesia. Out of the thirteen patients studied, an overwhelming majority, during SNP infusion, manifested a moderate enhancement in the stroke volume with simultaneous increase in the heart rate. Postoperatively, there was a definite reduction in the pulse rate as compared to the pre-SNP values but a moderate increase in the stroke volume persisted, during the same postoperative phase and maintained a stable cardiac output.

In the earlier investigations on deliberate hypotension in plastic surgery (Enderby, 1961), sequelae such as myocardial hypoxia, were encountered often as a consequence of inadequate ventilating techniques prevalent in contemporary anaesthesia. The persistent ganglion blockade caused often by trimetaphan and halothane in the work presented here could not be overlooked as the restoration of mean arterial pressure to preoperative or near preoperative level, was invariably delayed and the use of a plasma volume expander (dextran) was necessary in 7 out of 14 patients, while in the same seven patients, in an additional two cases the use of pressor agents became mandatory. After the application of nitroprusside, there was little difficulty to restore the mean arterial pressure to the pre-SNP or near pre-SNP levels, after simple discontinuation of SNP infusion. However due to administration of larger doses of fentanyl the apnoea had to be re-

versed with naloxane in nine out of thirteen patients. The vulnerability of brain in hypoxaemia as well as hypocarbia tends to be noxious to circulation in man (Cohen, Alexander, Smith, Reivich & Wollman, 1967) and in animals (Brown, Carlson, Ljunggren, Siesjö & Snider, 1974). The incidence of such possible happenings was eluded by routine administration of oxygen-rich gas mixtures and by evading profound hyperventilation during induced hypotension. In addition to the positive inotropic effect on the heart, the limb blood flow became augmented in all the patients investigated, while at the termination of anaesthesia it was encouraging to be able to communicate with a patient who was already awake. A recent investigation on circulatory changes in various organs including the kidney, has reasserted an improved blood flow during sodium nitroprusside infusion (Pagani, Vatner & Braunwald, 1978). The technical aspect of monitoring during SNP infusion, at first encounter, may appear fairly cumbersome. However, with little training and skill it is not an uphill task to overcome this difficulty. Its application in hip-arthroplasty has already been reported (Vazeery & Lunde, 1979), without ill-effects to the patients. In this communication an attempt has been made to evaluate the two popular hypotensive techniques in the plastic reduction of the hypertrophic breast, with the pros and cons. It is at the discretion of the reader to render his own judgement in electing either of the two methods.

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HAEMODYNAMIC CHANGES DURING NITROPRUSSIDE AND TRIMETHAPHAN
INFUSIONS WITH CONCURRENT MODERATELY HIGH DOSAGE FENTANYL
ANAESTHESIA: AN INVASIVE AND NONINVASIVE STUDY DURING HIP
ARTHROPLASTY

AFZAL K. VAZEERY, PER LUNDE AND ARVID HOGBERG

Departments of Anaesthesia, Cardiology and Orthopaedic Surgery,
Central Hospital of Rogaland, Stavanger, Norway.

ABSTRACT

Moderately high dosage fentanyl anaesthesia (fentanyl $18 \mu\text{g. kg}^{-1}$) with 50 per cent nitrous oxide in oxygen, was administered during a slow infusion of a 0.01 per cent sodium nitroprusside (SNP) in dextrose ($n=15$), or a 0.1 per cent trimethaphan (TMP) in dextrose ($n=14$) to patients undergoing Charnley's hip-replacement arthroplasty. The changes in cardiovascular dynamics were monitored by bio-electric impedance plethysmography before, during and after employment of the two hypotensive agents. The significant increase in the cardiac output (CO) during the application of SNP ($p < 0.025$), was attributed to both an augmentation ($p < 0.05$) in the heart rate (HR) and a minimal rise ($p < 0.2$) in the ventricular stroke volume (SV). The less significant increase in CO during the infusion of TMP ($p < 0.25$) was ascribed to a consistently accelerated HR ($p < 0.01$) as the SV diminished ($p < 0.025$). The blood flow in the forearm showed a marked increase during the SNP as well as the TMP infusion ($p < 0.01$), whereas the total peripheral vascular resistance (PVR) declined considerably under the two hypotensive techniques ($p < 0.001$). There was evidence of stable cardiac performance, as judged from a well preserved cardiac index (CI), in most of the patients in the both groups.

Key words: Induced hypotension, nitroprusside, trimethaphan, moderately high dosage fentanyl, haemodynamics, impedance plethysmography.

The rapid infusion of sodium nitroprusside as a hypotensive agent in procuring a blood-less surgical field,¹⁻⁴ or its use in the treatment of moderate essential hypertension⁵ and hypertensive crises,⁶ owes a great deal to meticulous efforts being made concurrently towards analysing its pharmacodynamics as a potent vasodilator.⁷⁻¹²

Whereas the problems encountered during profuse surgical haemorrhage under replacement of hip require due attention,^{13,14} there is sufficient evidence to suggest the merit of deliberate arterial hypotension in major orthopaedic surgery.¹⁵⁻¹⁹

The administration of large doses of fentanyl ($10 \mu\text{g. kg}^{-1}\text{min}^{-1}$), during experiments carried out upon dogs, by Bidwai. et al, did not incur any significant changes in the estimated plasma or the glomerular filtration rate.²⁰ A recent investigation conducted on man proposes that after the application of high doses of fentanyl ($16 \mu\text{g. kg}^{-1}$), there is little modification seen in the distribution of regional cerebral blood flow.²¹ Previously, we reported about a consistent cardiovascular stability during SNP infusion under deep neuroleptanaesthesia.²²

This investigation was designed to look for the impact, if any, on the haemodynamic variables by the moderately high doses of fentanyl in sustaining a deep analgesia during hypotension induced by a minimal dosage of SNP or TMP.

TABLE I

Patients treated for coxarthrosis under elective arterial hypotension induced by sodium nitroprusside (SNP) or trimethaphan (TMP) with conjunct high-dosage fentanyl anesthesia. (Data given as mean and range)

	SNP hypotension	TMP hypotension
No. of patients	15	14
Age (years)	68 (53-76)	69 (57-73)
Weight (kg)	66 (52-91)	64 (55-81)
Height (cm)	169 (160-183)	167 (164-181)
Hemoglobin (g %)	13.7(12.1-15.8)	13.5(12.4-16)
Hematocrit (pcv %)	39.8(37-46)	40.0(38-44)
Duration of operation (min)	96 (77-108)	94 (81-105)
Blood loss during surgery (ml)	303 (145-385)	297 (165-405)

TABLE II

Mean arterial pressure (MAP) in mmHg

	SNP hypotension Mean $\pm$ SEM	TMP hypotension Mean $\pm$ SEM
Before induction of anesthesia	92 $\pm$ 4 ^a	91 $\pm$ 5 ^b
During surgery	65 $\pm$ 2 ^c	64 $\pm$ 3 ^d
After termination of surgery	95 $\pm$ 4 ^e	84 $\pm$ 4 ^f
Difference a=e = 3 (not significant)		
Difference a=c =27 (P<0.01)		
Difference b=d =27 (P<0.01)		
Difference e=f =11 (P<0.05)		

PATIENTS AND METHODS

Twenty-nine patients undergoing hip arthroplasty for coxarthrosis were studied. Included were 21 women and 8 men, subdivided into two groups. In Group 1, the patients had deliberately controlled hypotension produced by SNP. In Group 2, the arterial hypotension was induced by TMP. A careful preoperative clinical screening excluded any patient showing a clear or suspected systemic, cardiovascular or cerebrovascular disease. The criteria laid down by the local Medical Ethical Committee for Human Research were strictly complied with. The age, sex, weight, as well as the haemoglobin, haematocrit and the duration of surgery were comparable in the two groups (Table I).

As premedication the patients received atropine 0.5 mg, promethazine 25 mg and pethidine 25-50 mg IM, one hour prior to the surgery. Anaesthesia was induced with fentanyl $6 \mu\text{g. kg}^{-1}$ (0.3-0.5 mg). Methohexitone was administered as a sedative in a dose of 0.5 mg. kg^{-1} (30-40 mg) and the endotracheal intubation was facilitated with d-tubocurarine (dTc) 0.4 mg. kg^{-1} (25-30 mg). Before the induction of anaesthesia the nature of the surgical operation and the scheduled hypotensive anaesthesia were explained to all the patients and their consent obtained.

For the measurement of MAP an indwelling cannula (venflon 1.2 mm, Viggo) was inserted into the radial artery while the CVP was monitored by placing a radio-opaque catheter (Drum-cartridge 1.8 mm, Venisystems) into the antebrachial vein. The MAP and the CVP were displayed constantly via a disposable Pressurveil transfer unit with a membrane depressor tube connected directly to the respective pressure gauge (Concept Inc.).

Five to seven minutes prior to the first surgical incision the infusion of SNP or TMP was started at a predetermined minimal rate of $25\text{-}30 \mu\text{g. kg}^{-1}\text{min}^{-1}$ for SNP, and $250\text{-}300 \mu\text{g. kg}^{-1}\text{min}^{-1}$ for TMP, via

an infusion pump (IVAC 981).

The supplementary doses of fentanyl (one half that of the induction dose) and dTc (5 mg) were given intermittently to maintain a state of deep analgesia and adequate muscle relaxation. The rate of infusion of the respective hypotensive agent was adjusted as necessary to maintain the MAP level at 60-65 mm Hg. The patients lay supine, inhaled 50 per cent nitrous oxide in oxygen. They were moderately hyperventilated via a Manley (Servovent) respirator.

A routine blood-gas analysis was conducted before, during and after the hypotensive anaesthesia and adjustments at the respirator were made, if necessary, to maintain a stable ventilation ($p\text{CO}_2$ range 3.7-4.5 kPa). Haematocrit values were obtained before, during and after surgery. The swabs were weighed intraoperatively. Blood loss from suction drainage was measured postoperatively. Blood loss during or after surgery was replaced promptly with the homologous blood. All patients received Ringer lactate 1.5 l and fructose-glucose solution (10 per cent) 1.0 l on the day of the operation.

The changes in the SV, HR and the ECG were monitored by Minnesota impedance cardiograph (Instrumentation of Medicine Inc. model 304 A), while the MAP and the CVP were read from the pressure gauges before, during and after the application of hypotensive drugs. Postoperative measurements were done at recovery room. For each SV estimation 4 tracings of the first derivative of the impedance cardiogram were taken into account. Six readings were made after a new calibration at each interval and a mean of these values calculated. The stroke volume was calculated by applying Kubicek's equation:

$$\Delta V = \rho \cdot \left(\frac{L}{Z_0} \right)^2 \cdot T \cdot (dz/dt)_{\min}$$
 where ΔV = the ventricular stroke volume (ml), ρ = the electrical resistivity of blood at 100 kHz (ohms-cm), L = the mean distance (cm) between the two inner electrodes

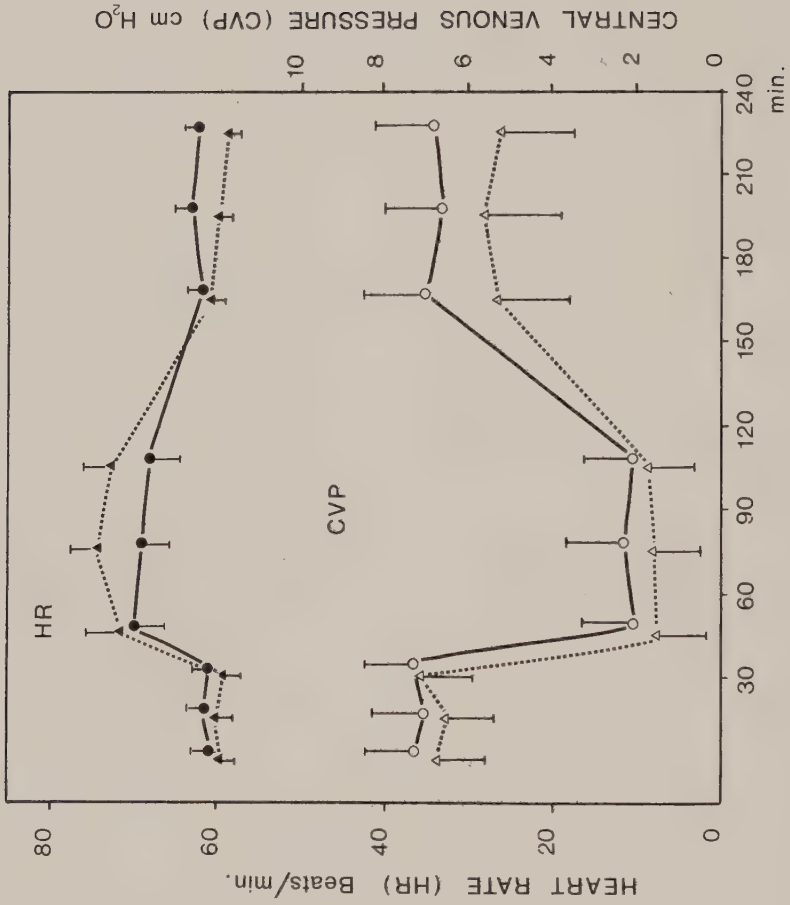


Figure 1. A profile of changes in heart rate (HR), and central venous pressure (CVP) during SNP or TMP infusion under moderately high dosage fentanyl anaesthesia. HR ●—● SNP, ▲—▲ TMP; CVP ○—○ SNP, △—△ TMP.

(measured front and back), Z_0 = the impedance in ohms, between the two inner (potential) electrodes, $(dz/dt)_{\min}$ = the minimum value of dz/dt occurring during the cardiac cycle (ohms. sec⁻¹), T = the ventricular ejection time in seconds, $CO = SV \times HR$. At each calculation the haematocrit was determined instantaneously and the corresponding value of μ obtained from a nomogram, was inserted into the aforementioned equation.

At the end of surgery the muscle paralysis was reversed with atropine 1.0 mg and neostigmine 2.5 mg IV, and the fentanyl induced respiratory depression by naloxone 0.2 mg IV. At recovery room all patients were allowed to inhale oxygen 2 l via a nasal catheter.

RESULTS

In Group 1, a low MAP of 60-65 mmHg was attained with an infusion rate of 1.5-2.5 $\mu\text{g. kg}^{-1}\text{min}^{-1}$ (Table I). Its restoration to within 5 per cent of the pre-SNP levels, at the end of surgery, was uneventful and accomplished soon after it was discontinued. During the use of a slow infusion of SNP with supplementary doses of fentanyl, abrupt fluctuations in the blood pressure were scant. In two patients the dosage of nitroprusside required to produce the low MAP was relatively much higher (5.6 & 3.8 $\mu\text{g. kg}^{-1}\text{min}^{-1}$) than the anticipated dose. In one case it was remarkably low (0.74 $\mu\text{g. kg}^{-1}\text{min}^{-1}$).

In Group 2, the desirable low levels of MAP, comparable to those of the former group, were attained without difficulty in a majority of patients at a rate of 15-30 $\mu\text{g. kg}^{-1}\text{min}^{-1}$ (Table II & IV). After discontinuing TMP infusion the restoration of MAP to within 15 per cent of the base-line (pre-TMP) values was reached in most of the patients. In 3 cases, however, the use of a plasma volume expander (dextran 70) became mandatory. There was no evidence of either a sudden fall or abrupt rise in the arterial pressure during the recovery stage in the two groups studied herein.

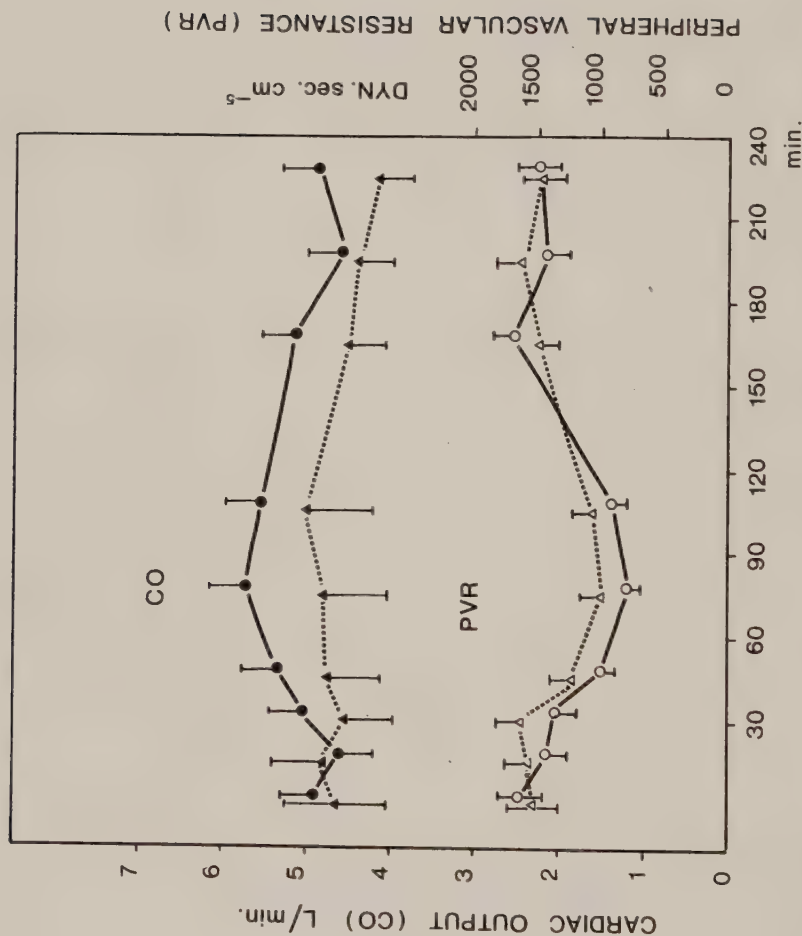


Figure 3. Impact of the hypotensive agents, SNP and TWP, on cardiac output (CO), and peripheral vascular resistance (PVR), during deep fentanyl anaesthesia.
CO ●—● SNP, ▲—▲ TWP; PVR ○—○ SNP, △—△ TWP.

TABLE III

Statistical comparison of cardiovascular variables before, during and after
SNP infusion (group I) with concomitant moderately high dosage fentanyl anaesthesia.

	I Before Mean $\pm$ SEM	II During Mean $\pm$ SEM	III After Mean $\pm$ SEM	% change between I & II	P value	% change between I & III	P value
MAP = Mean arterial pressure (mmHg)	92 $\pm$ 1.9	65 $\pm$ 1.2	95 $\pm$ 2.0	-30	< 0.01	+3.7	-
CVP = Central venous pressure (cmH ₂ O)	7 $\pm$ 0.2	2 $\pm$ 0.03	6 $\pm$ 0.1	-77	< 0.001	-8.1	-
HR = Heart rate (beats. min ⁻¹)	61 $\pm$ 1.2	69 $\pm$ 1.3	62 $\pm$ 1.1	+13	< 0.05	-	-
SV = Stroke volume (ml)	77 $\pm$ 1.8	79 $\pm$ 1.0	77 $\pm$ 1.2	+ 2.5	< 0.2	-	-
SVI = Stroke volume index (ml. beat ⁻¹ .m ⁻²)	44 $\pm$ 2.1	44 $\pm$ 1.8	45 $\pm$ 1.3	-	-	-	-
CO = Cardiac output (L. min ⁻¹)	4.8 $\pm$ 0.12	5.5 $\pm$ 0.11	4.7 $\pm$ 0.09	+14.5	< 0.025	-	-
CI = Cardiac index (L.min ⁻¹ .m ⁻²)	2.7 $\pm$ 0.08	3.1 $\pm$ 0.10	2.8 $\pm$ 0.07	+14.8	< 0.05	+3.7	< 0.4
SVR = Systemic vascular resistance (dynes. sec ⁻¹ .cm ⁻⁵)	1511 $\pm$ 31	927 $\pm$ 18	1581 $\pm$ 45	-38	< 0.001	-	-
OS = Oxygen saturation (%)	95 $\pm$ 1.9	94 $\pm$ 1.7	95 $\pm$ 2.7	-	-	-	-
AO = Available oxygen (ml. min ⁻¹)	744 $\pm$ 22	788 $\pm$ 31	780 $\pm$ 23	+5.9	< 0.2	+4.8	< 0.2
LBF = Limb blood flow (ml. min ⁻¹)	48 $\pm$ 1.3	83 $\pm$ 1.2	59 $\pm$ 1.7	+73	< 0.01	+23	< 0.05

P < 0.05-0.01 (significant), P < 0.01-0.001 (highly significant), student's t test n = 15

- (no difference)

Patients receiving SNP showed a moderate increase in the HR ($p < 0.05$). Those given TMP demonstrated an even greater rise in HR ($p < 0.01$) (Table III & IV) (Figure 1). After the induction of hypotension the HR was consistent in the two groups and no sudden change in rhythm was seen. The maximum heart beat recorded was $92 \cdot \text{min}^{-1}$ in a patient who received a greater amount of TMP ($41 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) than had been expected.

In SNP group, there was a minimal rise in SV in 12 patients ($p < 0.2$), decrease in one (5.6 per cent); in two the change was insignificant. In the TMP group, there was a definite decline in the mean SV in all patients given the drug ($p < 0.025$) (Table IV) (Figure 2)., although it was invariably accompanied by an accelerated HR. It returned to within 5 per cent of its pre-TMP values after the hypotensive infusion was stopped.

There was a moderate elevation of CO in the SNP group ($p < 0.025$) (Table III). The postoperative values of CO, when compared to the controls did not reveal any visible difference (Figure 3). The changes in CO, during TMP infusion were, nonetheless, less remarkable when compared with the base-line as well as the postoperative levels (Table III).

The LBF improved considerably during SNP and the TMP infusions ($p < 0.01$) (Figure 2). The drop in the calculated total PVR and the constantly measured CVP was highly significant in both the groups studied ($p < 0.001$) (Figure 3).

Of the 15 patients who received SNP, one showed a marked depression of the ST segment on the ECG. This patient had received $5.6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ of SNP. The depression became resolved within 24 hours. In another case the ST segment depression was transient and disappeared in the postoperative period (dosage, $3.8 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). None of the subjects showed a flattening or inversion of T waves.

TABLE IV

Statistical comparison of means of cardiovascular parameters before, during and after TMP infusion (group II) with concurrent moderately high dosage fentanyl anaesthesia

	I Before Mean $\pm$ SEM	II During Mean $\pm$ SEM	III After Mean $\pm$ SEM	% change between I & II	P value	% change between I & III	P value
MAP = Mean arterial pressure(mmHg)	91 $\pm$ 2.1	64 $\pm$ 1.5	84 $\pm$ 1.8	-29	< 0.01	+7	< 0.05
CVP = Central venous pressure(cmH ₂ O)	7 $\pm$ 0.05	1 $\pm$ 0.03	5 $\pm$ 0.05	-77	< 0.001	-22	< 0.01
HR = Heart rate (beats. min ⁻¹)	60 $\pm$ 1.4	73 $\pm$ 1.5	60 $\pm$ 1.6	+21	< 0.01	-	-
SV = Stroke volume (ml)	74 $\pm$ 1.5	65 $\pm$ 1.3	72 $\pm$ 1.1	-12	< 0.025	-3	< 0.2
SVI = Stroke volume index (ml. beat ⁻¹ .m ⁻²)	43 $\pm$ 0.9	37 $\pm$ 0.8	41 $\pm$ 1.1	-13	< 0.025	-4	< 0.4
CO = Cardiac output (L. min ⁻¹)	4.6 $\pm$ 0.1	4.8 $\pm$ 0.13	4.3 $\pm$ 0.09	+4	< 0.25	-6	< 0.5
CI = Cardiac index (L. min ⁻¹ .m ⁻²)	2.6 $\pm$ 0.09	2.7 $\pm$ 0.08	2.5 $\pm$ 0.1	+3	< 0.4	-3	< 0.4
SVR = Systemic vascular resistance (dynes. sec ⁻¹ . cm ⁻⁵)	1584 $\pm$ 29	1094 $\pm$ 30	1569 $\pm$ 42	-30	< 0.001	-	-
OS = Oxygen consumption (%)	96 $\pm$ 1.5	95 $\pm$ 1.8	95 $\pm$ 1.3	-	-	-	-
AO = Available oxygen (ml. min ⁻¹)	677 $\pm$ 17	742 $\pm$ 27	698 $\pm$ 32	-	-	-	-
LEF = Limb blood flow (ml. min ⁻¹)	50 $\pm$ 1.1	69 $\pm$ 1.2	51 $\pm$ 0.09	+37	< 0.01	-	-

P<0.05 (significant), P<0.01-0.001 (highly significant), student's t test n = 14

- (no difference)

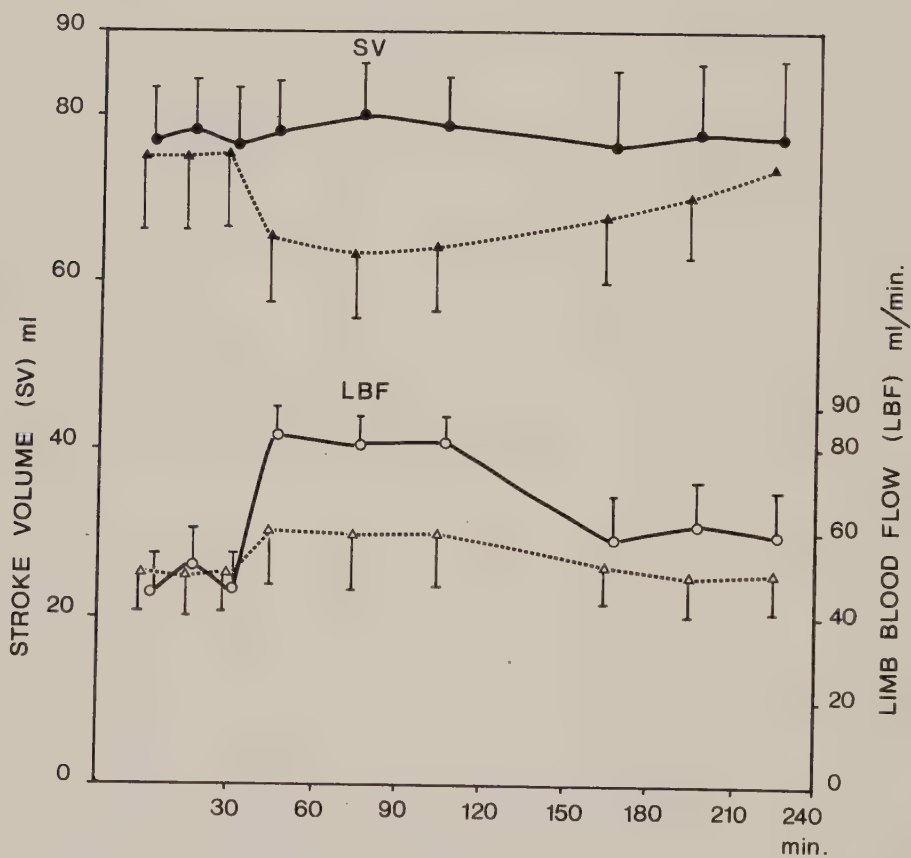


Figure 2. Effects of SNP- or TMP-induced hypotension on stroke volume (SV), and limb blood flow (LBF) under deep fentanyl anaesthesia. SV ●—● SNP, ▲—▲ TMP; LBF O---O SNP, Δ---Δ TMP.

Fourteen patients who received TMP demonstrated a 23 per cent incidence of ST segment depression (mean dosage, $27 \mu\text{g. kg}^{-1}\text{min}^{-1}$). The ECG changes observed during the TMP infusion were resolved within 24-72 hours after discontinuing infusion. There was no clinical evidence suggesting myocardial infarction, renal or cerebrovascular pathology during the average postoperative stay of 22 days in the hospital in any of the patients studied. The blood gas analysis showed a decline in the values of pO_2 during SNP only, in 2 patients (5.5 & 7.3 per cent). They recovered to their control values in the recovery room. The fall in the oxygen content was not related to SNP dosage. There was no incidence of respiratory depression postoperatively, and no further naloxone was needed in any of the patients studied.

DISCUSSION

In the study reported herein, a combination of moderately high dosage fentanyl anaesthesia and SNP created a stable cardiac performance with sustained ventricular stroke work and a moderate rise in HR. There was no evidence of any abrupt changes in the heart rhythm or sudden fluctuations in the MAP. The rebound hypertensive episodes seen after the discontinuation of nitroprusside, which has been reported by some workers,²³ were invariably absent.

The mean dosage of SNP used in the present investigation was reduced to one fourth of the amount used in similar operations that were performed under light balanced anaesthesia, as reported earlier.¹⁸ It was noted, however, that the effects of SNP during deep fentanyl anaesthesia on the cardiovascular dynamics of older age group patients are often very different in their magnitude when compared to those of their younger counterparts.²²

The acceleration of heart action, which is a potential end-result of a vagal withdrawal, if excessive, can be reduced partially via the induction of a beta adrenergic receptor blockade.⁵ Excessive

tachycardia was not encountered in any of the two groups studied. A moderate tachycardia seen in our patients could have been caused by an initial higher dose of dTc (25-30 mg) and it may as well have contributed significantly towards hypotension.

Fentanyl, which is a potent analgesic, tends to hold the renal, cardiovascular and cerebrovascular haemodynamics within normal thresholds in doses ranging from 5-16 $\mu\text{g. kg}^{-1}$ ^{20,21} Its application in moderate doses produced desirable hypotension with minimal doses of the two hypotensive agents.

Scott and co-workers demonstrated that trimethaphan does not cause suppression of cardiac function during infusion under the inhalation of halothane.²⁴ Its application under deep fentanyl anaesthesia showed no significant changes in the repeatedly monitored cardiovascular dynamics. At the end of surgery, however, we noticed in three patients that, without the aid of a plasma volume expander it failed to establish a prompt restoration of MAP to the control values.

The electrical impedance plethysmography technique, being noninvasive, proved convenient in monitoring the changes in SV, HR and CO repeatedly. Several workers have investigated the reliability of the measurement of cardiac output by the impedance method.²⁵⁻²⁸ They found that overestimations are frequent when the absolute values are compared with the isotope dilution techniques. Although it is considered to be less precise in absolute terms than the invasive techniques, the results can be reproduced and are comparable with the thermodilution methods.²⁹ It is thought essential to determine the blood resistivity corresponding to a known value of the haematocrit, thereby improving accuracy in calculation of stroke volume.^{30,31} The general consensus is that the changes in magnitude are accurate and comparable with the invasive methods.^{27,29}

The impedance cardiography provided the additional advantage of simultaneously monitoring the electrocardiographic changes, in our investigation. The incidence of the ST segment depression, seen in two of our patients during the SNP infusion, was probably the result of a relatively higher dosage of the vasodilator, as no other possible interpretation could be put forward. In Group 2, the more frequent occurrence of the ST segment depression was also related to a higher dosage of TMP. The depression of the ST segment and a flattening or inversion of T waves, have been reported by Fahmy³² Less ischaemic changes detected by us under a minimal amount of SNP, might support the hypothesis that the myocardial circulation is probably modified when an optimal dosage of this agent is exceeded. Our supposition is assisted by the additional fact that fentanyl, which was an important determinant in securing a satisfactory state of hypotensive anaesthesia, is thought to be incapable of causing any ECG changes in large doses.³³

Thus on the basis of our data, we suggest that induced hypotension with minimal amounts of nitroprusside or trimethaphan, administered over underlying anaesthetic of N_2O , O_2 and moderately high doses of fentanyl is safe and efficacious.

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Sodium Nitroprusside as a Hypotensive Agent in Surgery:

Determination of the Minimum Dosage Requirement with Moderately
High Doses of Fentanyl

A. K. Vazeery, K. Aspelund, S. Skeie and S. Sydnes

Departments of Anaesthesiology, Plastic Surgery, Orthopaedic
Surgery and Clinical Biochemistry, Central Hospital of Rogaland,
Stavanger, Norway.

Sodium nitroprusside (SNP) was used as a hypotensive agent with 47 patients undergoing diverse kinds of surgery. It was employed as an 0.01 per cent solution in 5 per cent glucose in patients (n=23) who were receiving a balanced anaesthesia with fentanyl (mean dosage, $9.5 \mu\text{g. kg}^{-1}$) as the main analgesic agent (Group I). A comparison was made with patients (n=24) undergoing similar surgical procedures under hypotension induced by SNP, but receiving a moderately high-dosage fentanyl (mean dosage, $18 \mu\text{g. kg}^{-1}$) anaesthesia (Group II). An arterial blood gas analysis was conducted during the operation and post-operatively, while the serum levels of sodium thiocyanate were determined during SNP infusion and after the surgery. It was noted that by increasing the dosage of fentanyl to twice the amount required in a light balanced anaesthesia, one could conveniently reduce the dosage of sodium nitroprusside required in a short-term infusion to 0.3 mg. kg^{-1} or $3.6 \mu\text{g. kg}^{-1} \text{ min}^{-1}$.

Deliberate hypotension combined with general anaesthesia has been practised in surgery in various forms since 1946, when Gardner introduced it by the method of arteriotomy. Shortly thereafter hypotension was attained by total spinal block for different surgical procedures (Griffiths & Gillies 1948). Several hypotensive agents have been used during the last four decades to minimize surgical haemorrhage. Laborious efforts have been made to keep the haemodynamics and blood chemistry of the patients subjected to deliberate arterial hypotension within the physiological realm.

The necessity of having a drug which did not have the hazard of higher doses of ganglion-blocking agents led to the clinical application of sodium nitroprusside in recent years. Toxicity has been encountered several times due to inadvertent overdosage in SNP-induced hypotension (Merrifield & Blundell 1974, Jack 1974, MacRae & Owen 1974, Davies et al. 1975) or after prolonged therapy (Nourok et al. 1964). Nitroprusside has been recommended recently in a dose not exceeding 1.5 mg. kg^{-1} during short term infusions (Vesey et al. 1976).

In an investigation which was reported earlier (Vazeery et al. 1980) it was observed that during SNP infusion and deep neurolept-anaesthesia, the haemodynamic status of the patients was well preserved. Hence this study was planned to determine the minimal dosage of nitroprusside with moderately high doses of fentanyl. A meticulous watch on the patients was kept through the blood gas and serum thiocyanate analysis.

PATIENTS AND METHODS

47 patients undergoing major orthopaedic or plastic reconstructive surgery were studied. There were 17 male and 30 female patients included in this investigation. All of them were receiving

methohexitone-fentanyl-curare- N_2O and oxygen anaesthesia. They were randomized into two groups. The patients were all normovolaemic and the age, weight, sex, haemoglobin and the nature of surgery were comparable in both groups (Group I, mean age 51 range 20-76 years, Group II, mean age 49 range 19-73 years). It was ascertained that all the patients receiving SNP had no evidence of cerebrovascular, cardiovascular or kidney disease (Controlled hypotension has been employed at this clinic since 1971 for various indications and the same criteria have been strictly observed). Before application of SNP the entire procedure was explained and patient consent obtained. Premedication was atropine 0.5 mg, pethidine 25-50 mg and promethazine 25 mg given an hour before the operation.

In Group I, induction was made with methohexitone 60-100 mg and fentanyl 0.1-0.2 mg whereas in Group II, prior to induction with methohexitone 30-50 mg, an intravenous injection of fentanyl 0.3-0.5 mg ($6 \mu\text{g. kg}^{-1}$) was given. Orotracheal intubation was facilitated with d-tubocurarine (dTc) 30 mg, and analgesia was provided with supplementary doses of fentanyl (one half that of the induction dose), and muscular relaxation with dTc (5 mg). Prior to SNP infusion it was made sure that all patients were supine and the ECG was being monitored on an oscilloscope, which also acted as a pulse monitor. An indwelling cannula (venflon 1.4 mm, Viggio) was inserted into the radial artery and mean arterial pressure (MAP) was recorded continuously on a screen (Hewlett Packard). All patients received an isotonic solution of electrolytes, Ringer acetat 1.0 l and fructose-glucose 10 per cent 1.5 l on the day of operation. Infusion of 0.01 per cent sodium nitroprusside in 5 per cent glucose was made available through an infusion pump (IVAC 981). Continuous rectal temperature monitoring was carried out with a thermocouple due to the fairly cold environment of the

TABLE I

DOSAGE of FENTANYL (F) and SODIUM NITROPRUSSIDE (SNP)

FENTANYL ($\mu\text{g} \cdot \text{kg}^{-1}$)	<u>GROUP I, n = 23</u>		SNP $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	DURATION OF SURGERY (min)
	TOTAL SNP (mg)			
9.5 ± 0.04	48 ± 1.4		8.5 ± 0.3	82 ± 1.9
	<u>GROUP II, n = 24</u>			
18 ± 0.1	21 ± 0.9		3.6 ± 0.04	84 ± 2.1
Mean values $\pm$ S.E.M.				
Difference I-II (F) $P < 0.001$				
Difference I-II (SNP) $P < 0.001$				

DOSAGE COMPARISON OF FENTANYL AND SNP

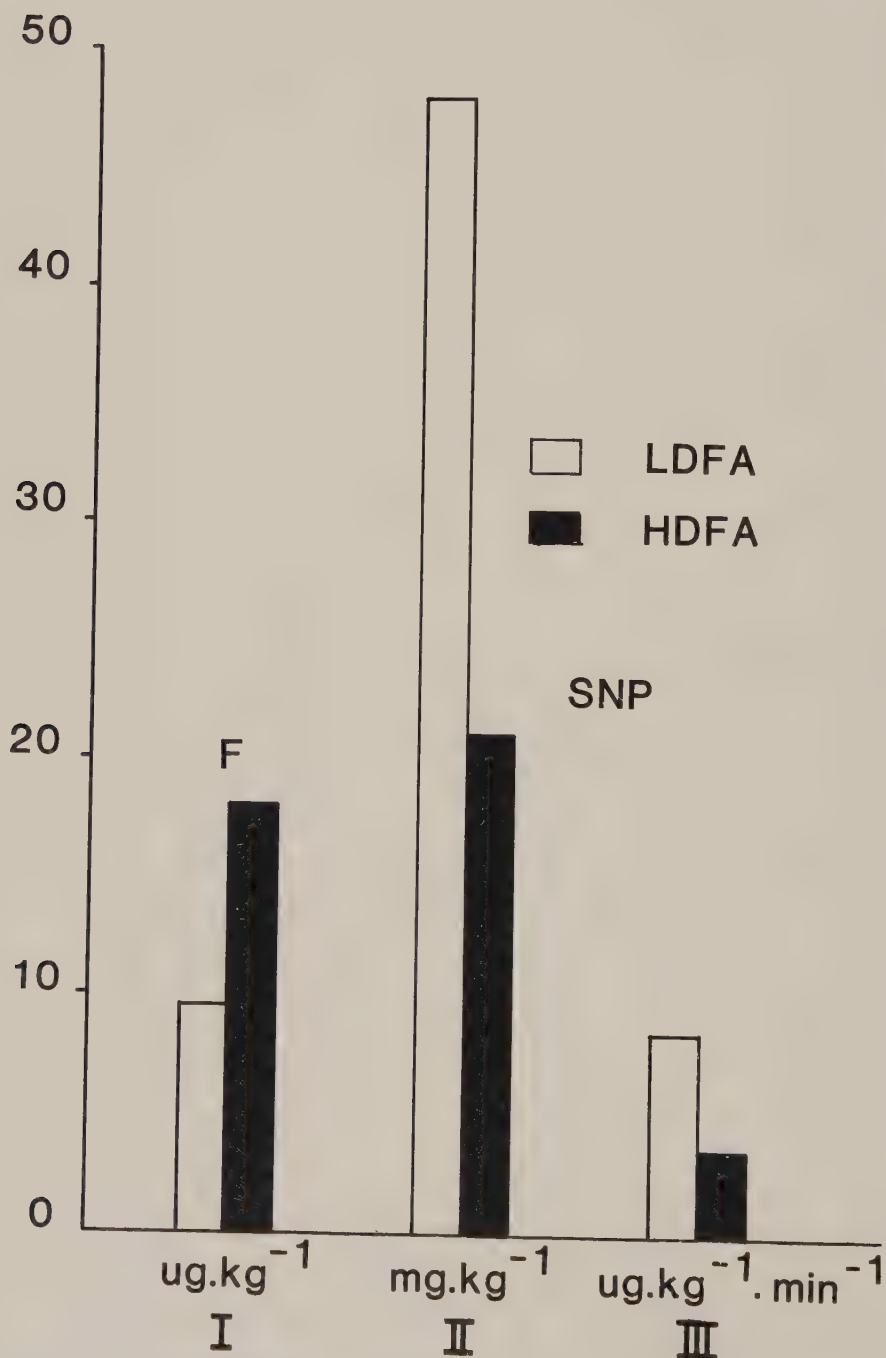


Fig. 1. Comparison of total dosage of fentanyl (F, I), and sodium nitroprusside (SNP, II), consumed in the 2 groups. III indicates the amount of SNP. kg⁻¹.min⁻¹ (LDFA, low dosage fentanyl anaesthesia; HDFA, high dosage fentanyl anaesthesia).

operation room.

Before starting SNP infusion, arterial specimens of blood were collected for blood gas analysis to provide comparison figures with values obtained during surgery. Further arterial blood samples were taken at intervals of 15 and 45 minutes, and 3 hours after the start of SNP infusion. SNP infusion was started 5 minutes before the first surgical incision and was regulated so that the MAP was maintained throughout at a level of 60-65 mm Törr.

Balanced anaesthesia was maintained with a mixture of 40 per cent oxygen in nitrous oxide, adequate muscle relaxation, moderate hyperventilation and additional doses of fentanyl as necessary (Group I). Halothane was used only as an adjunct when all other efforts failed to obtain the desired low level of MAP. In Group II, a moderately high-dosage fentanyl analgesia was maintained while the patients inhaled 50 per cent nitrous oxide in oxygen and were moderately hyperventilated.

For Sodium thiocyanate (SCN) serum determinations, specimens from 12 patients in each group were collected before the SNP infusion and 15 minutes, 45 minutes, 3 hours and 24 hours after. This was determined by the method described by Aldridge (1945). In addition blood samples from 12 patients admitted to the hospital for diverse ailments and not receiving nitroprusside, were analysed for SCN levels in the blood.

RESULTS

After an initial infusion rate of $100 \mu\text{g. min}^{-1}$ there was a considerable variation in need for SNP during the surgical procedure. It varied from $2.4 \mu\text{g. kg}^{-1} \text{ min}^{-1}$ in Group I, and from 1.1 to $7.4 \mu\text{g. kg}^{-1} \text{ min}^{-1}$ in Group II. The total requirement ranged from 0.2 mg. kg^{-1} to 1.3 mg. kg^{-1} in Group I, while it was considerably reduced in Group II where the need ranged from 0.1 mg. kg^{-1} to 0.6

BLOOD GAS ANALYSIS

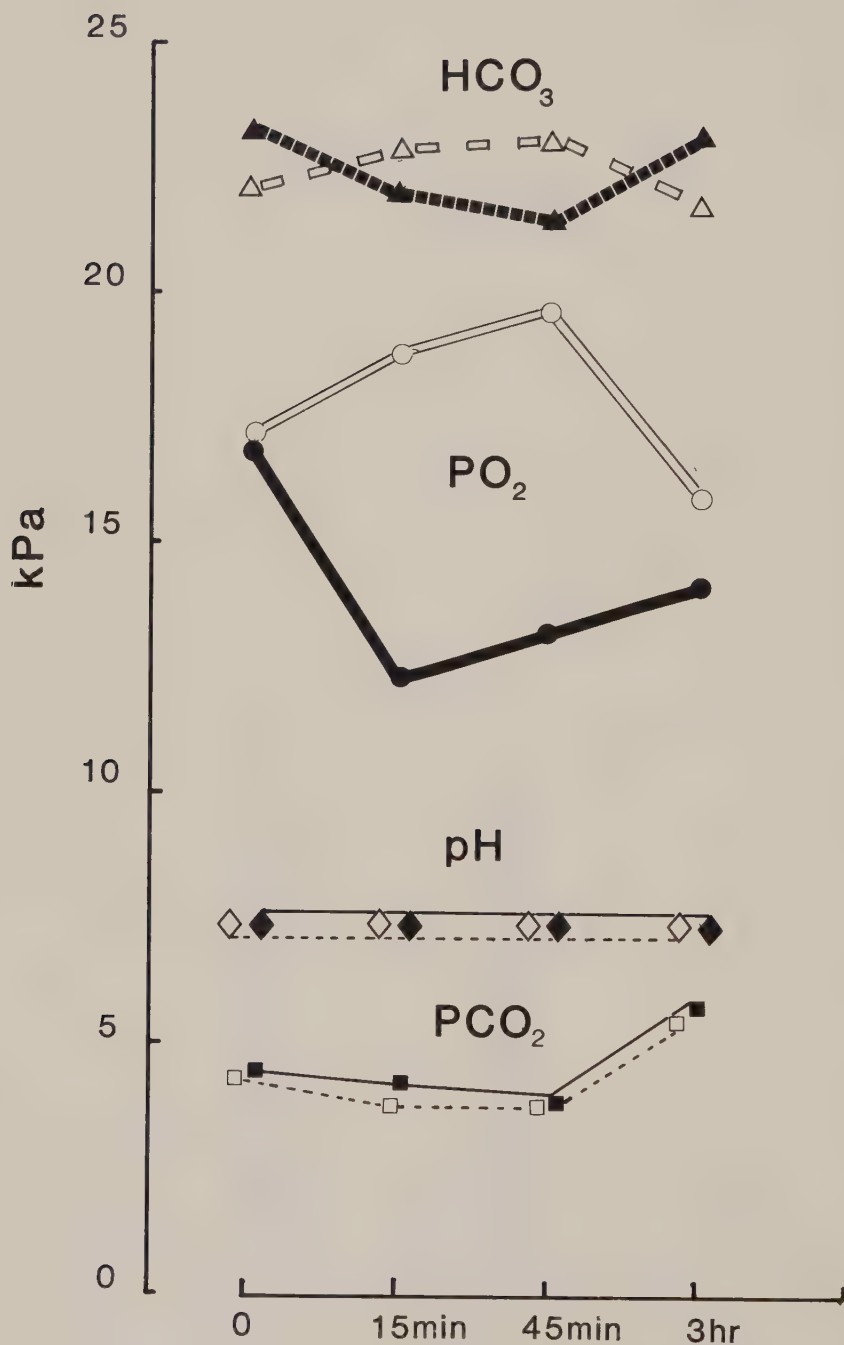


Fig. 2. Blood gas analysis before, during SNP infusion at 15, 45 min intervals and after 3 hr and 24 hr intervals (Δ , $\triangle$, $\bullet$, $\blacklozenge$, $\blacksquare$, indicate LDFA, and $\triangle$, $\triangle$, $\circ$, $\diamond$, $\square$, show HDFA).

TABLE II

ARTERIAL BLOOD-GAS ANALYSIS BEFORE, DURING and AFTER ADMINISTRATION OF SODIUM NITROPRUSSIDE (SNP)

GROUP I, n = 23											
BEFORE SNP			DURING SNP (15 mins)			DURING SNP (45 mins)			POSTOPERATIVE 3 HOURS AFTER SNP		
I			II			III			IV		
PH	PO ₂	PCO ₂ HCO ₃ BE	PH	PO ₂	PCO ₂ HCO ₃ BE	PH	PO ₂	PCO ₂ HCO ₃ BE	PH	PO ₂	PCO ₂ HCO ₃ BE
7.44	16.9	4.4 23.2 2.1	7.41	12.3 4.3	21.9 3.0	7.43	13.2 3.9	21.4 2.9	7.39	14.2 5.9	23.1 3.4
+0.02	+1.2	+0.1 + 0.8	+0.02	+0.9	+0.1 + 0.5	+0.01	+1.2	+0.1 + 0.6	+0.02	+0.7	+0.08 +0.7
GROUP II, n = 24											
V			VI			VIII			VIII		
7.45	17.2	4.2 22.1 1.7	7.48	18.8 3.9	22.8 3.5	7.49	19.6 3.8	22.9 3.2	7.38	15.9 5.6	21.7 1.1
+0.01	+2.1	+0.2 + 1.0	+0.03	+1.2	+0.1 + 0.6	+0.01	+1.3	+0.1 + 0.5	+0.006	+0.6	+0.08 +0.5

Difference I-II PO₂ = ***, BE = *Difference I-III PO₂ = *, PCO₂ = *Difference I-IV pH = *, PO₂ = *, PCO₂ = **, BE = **Difference V-VI pH = *, PO₂ = *, PCO₂ = *, BE = *Difference V-VII pH = *, PO₂ = *, PCO₂ = *, BE = *Difference V-VIII pH = **, PO₂ = *, PCO₂ = **, BE = *

* P= 0.05-0.01

** P= 0.01-0.001

*** P= < 0.001

Mean values in kPa ± S.E.M.

mg. kg⁻¹. The average total dose of 48 mg in Group I was reduced to a mean of 21 mg in Group II (Table I) (Fig. 1). It was noted that the younger age group patients needed relatively higher dosages. In 4 patients of Group I, supplementary halothane (0.5-1.0 per cent) was added to decrease the MAP from 70-75 mmHg to the desired 60-65 mmHg. In Group II the infusion rate of SNP was reduced to the minimal desired level with supplementary doses of fentanyl given intermittently.

There was a significant decrease in the dosage requirement of fentanyl, in the 2 groups studied. The mean dosage was 9.5 μ g. kg⁻¹ in patients receiving balanced anaesthesia, compared to 18 μ g. kg⁻¹ in patients who were given moderately high dosage fentanyl anaesthesia. The administration of relatively higher doses of fentanyl culminated in needing naloxone at the end of surgery, in all patients belonging to Group II.

The majority of patients in Group I, showed a significant increase in heart rate (mean increase of 26 per cent). Conversely, in the group who received deep fentanyl anaesthesia and minimal amount of nitroprusside, the increase in heart rate was moderate (11 per cent). The heart rate returned to pre-SNP levels in all patients 7-10 minutes after discontinuing its use.

The mean arterial pressure was restored to pre-SNP, or near pre-SNP levels, 7-10 minutes after the discontinuation of the infusion. No vasopressor agent was needed at the end of surgery, in contrast to its need after higher doses of trimethaphan or higher concentrations of halothane.

As all the patients were being moderately hyperventilated, there was a tendency seen towards mild respiratory alkalosis, and a steady increase in oxygen content particularly in the younger age group of patients. In Group I, there was a mean decrease of 18

TABLE III

SODIUM THIOCYANATE ESTIMATION IN HUMAN SERUM BEFORE, DURING AND AFTER SODIUM NITROPRUSSIDE (SNP)

BEFORE SNP	GROUP I, n = 12		AFTER SNP (3 hrs)	AFTER SNP (24 hrs)
	DURING SNP (15 mins)	DURING SNP (45 mins)		
I	II	III	IV	V
0.076 +0.007	0.104 +0.016	0.091 +0.011	0.081 +0.012	0.068 +0.009
GROUP II, n = 12				
VI	VII	VIII	IX	X
0.072 +0.007	0.092 +0.009	0.088 +0.01	0.076 +0.006	0.070 +0.006
SERUM LEVELS OF THIOCYANATE				
NOT HAVING SNP (n = 12)				
0.074 +0.009				

Difference I-II ***
 Difference I-III **
 Difference VI-VII **
 Difference VI-VIII **

Mean values in mmol. l⁻¹ + S.E.M
 * P = 0.05-0.01
 ** P = 0.01-0.001
 *** P < 0.001

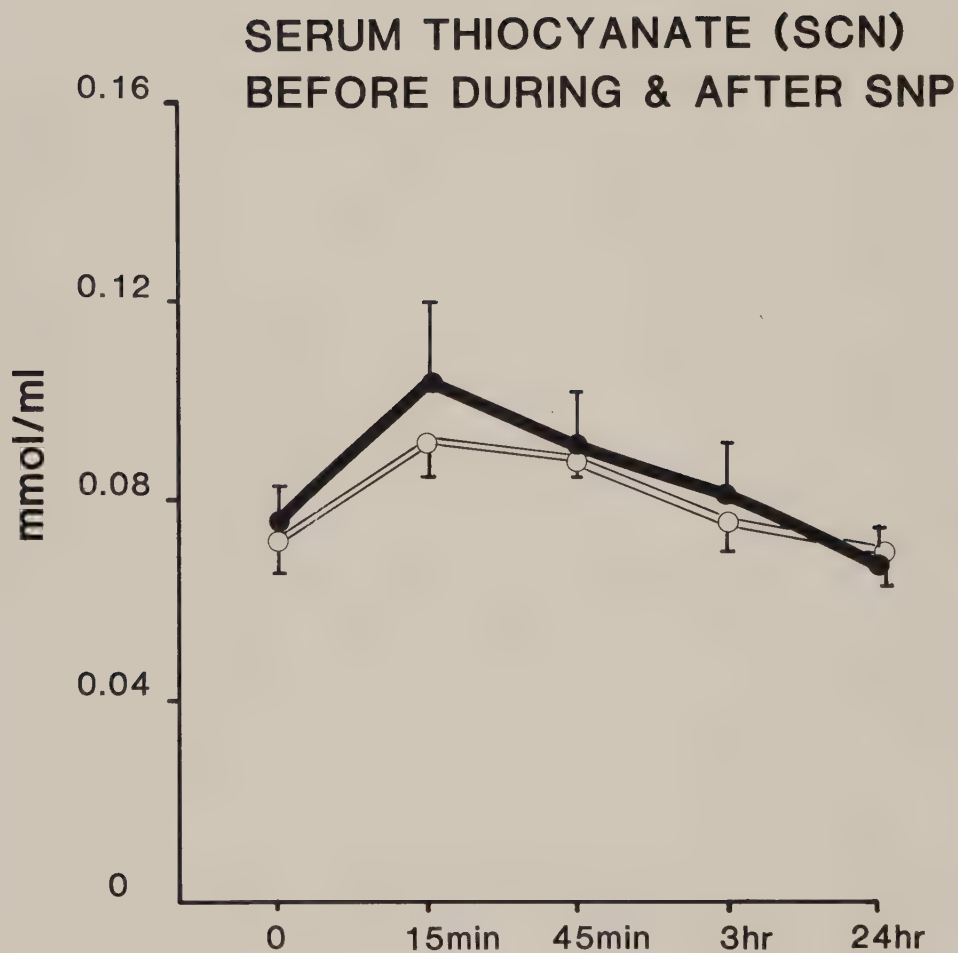


Fig. 3. Serum SCN concentrations during LDFA and HDFA before, during and at 15, 45 min intervals, and after at 3 hr and 24 hr intervals (●—● indicates LDFA, and ○—○ shows HDFA).

per cent in 9 cases, while a mean reduction of 11 per cent was noted in two patients in Group II. The reductions were not related to the age but a clear link existed between the decrease of pO_2 and the amount of SNP administered.

The changes in the acid-base status of the patients seen postoperatively were remarkable when compared with the pre-SNP levels ($P < 0.01$) (Table II, Fig. 2). Evidently this was due to the pre-SNP gas analysis being conducted immediately after intubation while patients were being ventilated artificially. The pCO_2 values rose fairly rapidly after extubation particularly in the elderly patients. Nevertheless, the blood chemistry was found to be within normal clinical levels.

Twelve patients in each group, which were chosen at random showed initial increments in serum levels of SCN (Fig. 3). However, 45 minutes after beginning SNP infusion there was a fall in SCN levels in 3 patients of Group I and 7 cases belonging to Group II. In the second group 3 individuals showed values well below the controls. The values of SCN, 24 hours after SNP administration, fell below the control values in the other 4 patients in Group II.

The 12 patients selected at random who were in-patients at the hospital and not receiving nitroprusside, did not show any remarkable difference in their SCN levels (mean = 0.78 mmol) as compared with those who were being treated with SNP (Table III).

All the patients investigated were subsequently discharged from the hospital without any evidence of disturbance in the cardiovascular, hepatic or renal system, or any overt abnormal behaviour.

DISCUSSION

After an extensive study of its applications in experimental animals, Johnson (1928, 1929) suggested the clinical use of nitroprusside, and cited encouraging results after treating three patients. He believed its metabolic pathway was through thiocyanate, not cyanide. Its metabolic pathway through thiocyanate, as well as cyanide, was demonstrated by Goldstein & Rieders (1953) and this has been recently confirmed (Vesey et al. 1976).

Due to the serious consequences after an inadvertent overdosage (Jack 1974, Davies et al. 1975) many who were enthusiastic about hypotensive anaesthesia are still reluctant to handle this agent. The major concern has been uncertainty as to maximum dosage. The dosage suggested by McDowall and his colleagues (1974), i.e. a maximum rate of $1.6 \text{ mg. kg}^{-1} \text{ hr}^{-1}$ or $26 \text{ ug. kg}^{-1} \text{ min}^{-1}$ is not valid when viewed in context with estimations of cyanide in serum under SNP administration (Vesey et al. 1976). They recommended not exceeding a dosage of 1.5 mg. kg^{-1} and supplement it with halothane if necessary rather than increasing the SNP infusion. In the study reported herein, the Group I patients were submitted to the aforementioned technique. In Group II, however, we never found it necessary to exceed the optimal dose of $10 \text{ ug. kg}^{-1} \text{ min}^{-1}$ suggested by Greiss et al (1976), when hypotensive anaesthesia was being maintained with moderately high dosage fentanyl. The mean was $3.6 \text{ ug. kg}^{-1} \text{ min}^{-1}$ ($n=24$), an eminently reasonable figure. This dosage should interest those noting the dosage used by Vesey et al. Their range was from a minimum of $5.1 \text{ nmol. kg}^{-1} \text{ min}^{-1}$ to a maximum of $44.9 \text{ nmol. kg}^{-1} \text{ min}^{-1}$.

The anaesthetic technique included moderate hyperventilation in all patients since there is apparently an additional advantage of curtailing the amount of anaesthetic agents being employed (Bodman 1967).

pCO₂ levels were not allowed to fall below 3.5 kPa, a safe and compatible figure for short term hypotensive anaesthesia. Large doses of fentanyl are not only hypotensive, but can cause muscular rigidity probably through their actions on the central nervous system (Sokoll et al. 1972). This effect can be successfully reversed by naloxone at the end of surgery.

Reductions of oxygen content which was frequent in Group I patients and has been observed by us earlier (Vazeery & Lunde 1979), was initially documented by other investigators (Wildsmith et al. 1975). Its occurrence as well as magnitude, however, seems to be related directly to the amount of SNP administered as it was observed only in 2 cases when a minimal amount of nitroprusside infusion had been given (Group II).

During nitroprusside induced hypotension we found no depression of cardiovascular haemodynamics under deep neuroleptanaesthesia (Vazeery et al. 1980). Based on this investigation, same moderately high doses of fentanyl were employed during minimal SNP infusion in the study reported herein, without ill effects.

Plasma thiocyanate concentrations in serum during SNP administration appeared to be an unreliable guide in the assessment of its dosage in short term infusions.

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CHANGES IN CARDIAC OUTPUT AND SYSTEMIC BLOOD PRESSURE
AFTER INSERTION OF ACRYLIC CEMENT DURING TRIMETHAPHAN,
SODIUM NITROPRUSSIDE AND GLYCEROL TRINITRATE (NITROGLYCERIN)-
INDUCED HYPOTENSION: A COMPARISON WITH CHANGES DURING NORMOTENSION

A. K. VAZEERY, S. SKEIE, AND O. ANDA

A. K. Vazeery, M. D.; Department of Anaesthetics;
S. Skeie, M. D.; O. Anda, M. D.; Department of Orthopaedic
Surgery, Central Hospital of Rogaland, N-4000 Stavanger, Norway.

SUMMARY

The effects of implantation of the acrylic monomer on the cardiovascular response were studied in 37 patients undergoing hip arthroplasty and receiving high-dosage fentanyl anaesthesia under normotension or during hypotension induced by trimethaphan (TMP), sodium nitroprusside (SNP), or glycerol trinitrate (GTN). The heart rate (HR), the mean arterial pressure (MAP), the ventricular stroke volume (SV), and the cardiac output (CO) were monitored before and at 1, 2, 4, 6, 8 min intervals after the insertion of the acrylic cement into the acetabulum or the neck of femur. There was a moderate fall in the MAP after its insertion into the acetabulum under normotension and TMP-induced hypotension, while the reduction in pressure was significant after the cement's application in the femur. There was no abrupt change seen in the HR upon the implantation of the monomer in any of the patients investigated. Moderate reductions of the SV and the CO were observed during normotension or TMP hypotension. The changes in the cardiovascular dynamics on the insertion of the acrylic material were insignificant under hypotension induced by SNP or GTN.

Considerable interest has developed during recent years in the use of acrylic bone cement which is employed for stabilisation of joint in hip arthroplasty. Homsy and his associates (1972) demonstrated a substantial toxicity after a definite, but small leakage of acrylic monomer from the surgical wound to the central venous circulation. This toxicity of the acrylic material has been ascribed to its potential cardiocirculatory depressant action (Charnley, 1970; Powell et al., 1970; Cohen and Smith, 1971; Phillips et al., 1971; Newens and Voltz, 1972; Kim and Ritter, 1972; Kepes et al., 1972; Modig et al., 1975).

Deliberate arterial hypotension during hip arthroplasty is becoming more popular following the introduction of newer and reliable vasodilators, which render it more controllable (Lawson et al., 1976; Fahmy, 1978; Vazeery and Lunde, 1979; Barbier-Böhm et al., 1980; Rosberg, Fredin and Gustafson, 1982).

There is now a considerable body of literature depicting the changes in systemic arterial pressure and cardiac output, on the insertion of acrylic monomer during the hip arthroplasty. There is, however, not enough information yet available to describe any potential effects of the acrylic cement on these vital parameters in man, during controlled hypotension with trimethaphan, nitroprusside or nitroglycerin. Hence, this study was designed to investigate the possible effects of the monomer on human haemodynamics, during the hypotension induced by the three commonly used hypotensive drugs.

Table I. Patients treated for coxarthrosis under normotension (NTN) or deliberate hypotension induced by trimethaphan (TMP), sodium nitroprusside (SNP) and glycerol trinitrate (GTN).

(data given as mean)

	NTN	TMP	SNP	GTN
No. of patients	11	9	9	8
Age (yr)	68	68	69	65
Wt (kg)	65	69	68	65
Ht (cm)	170	166	167	167
Haemoglobin (g%)	13.7	12.9	12.5	13.6
Haematocrit (pcv%)	38.8	37.4	39.3	38.6
Duration of surgery(min)	98	101	95	99
Dosage of hypotensive drugs (mg kg ⁻¹)	-	1.7	0.14	0.16
Dosage of fentanyl (ug kg ⁻¹)	19	18	18	20
Intraoperative pO ₂ (kPa)	19.37	20.54	21.92	22.21
Intraoperative pCO ₂ (kPa)	4.12	4.32	4.18	4.20

MATERIAL AND METHODS

Thirty-seven patients, 25 women and 12 men, who were undergoing hip arthroplasty were studied. They were subdivided into 4 groups. The age, weight, duration of operation, sex, haemoglobin and haematocrit were comparable in these groups (Table I).

In group 1, which also served as control, the patients were operated on under normotension. In group 2, 3, and 4, the patients underwent surgery under controlled hypotension induced with TMP, SNP or GTN, respectively. A pre-operative clinical evaluation excluded any patient with cardiovascular, renal or cerebrovascular disease. An informed consent was obtained prior to surgery in all cases.

The patients were premedicated with atropine 0.5 mg, promethazine 25 mg and pethidine 25 mg i.m. 1 hr before the operation. Induction was done with i.v. fentanyl 0.3-0.5 mg ($6 \mu\text{g kg}^{-1}$) and methohexitone sodium 30-40 mg (0.5 mg kg^{-1}). The endotracheal intubation was facilitated with d-tubocurarine 25-30 mg (0.4 mg kg^{-1}).

For the constant measurement of the MAP an indwelling cannula (venflon 1.2 mm, Viggio) was inserted into the radial artery, and via a disposable Pressurveil transfer unit with membrane depressor tube, it was connected to an arterial gauge (Concept Inc.). Throughout the surgery, the pulse and e.c.g were monitored continuously by a cardioscope (Hewlett Packard model 7803 B and 78203 A).

Supplementary doses of fentanyl (one half that of the induction dose) and d-tubocurarine (5 mg) were given intermittently to all the patients to maintain a state of deep analgesia and adequate muscle relaxation. The patients lay supine, inhaled 50 % nitrous oxide in oxygen and were ventilated with a Manley (Servovent) respirator. Hypotension was induced in group 2 with 0.1 % TMP, in group 3 with 0.01 % SNP, and in group 4 with 0.01 % GTN. Infusions

were prepared by mixing the hypotensive drugs with 5 % glucose. 5 min prior to the first surgical incision the infusions of SNP or GTN were started at a pre-determined rate of $25-30 \mu\text{g min}^{-1}$ in the case of SNP or GTN, and $250-300 \mu\text{g kg}^{-1}$ for TMP, via an infusion pump (IVAC 981). All patients received an isotonic solution of electrolytes (Ringer acetate, Travenol) 1.5 l and 10 % fructose-glucose mixture (Invertose, Travenol) on the day of the operation. A routine blood-gas analysis was conducted before, during and after the anaesthesia and during controlled ventilation the adjustments, if necessary, were made at the respirator through the interposition of a Wright's spirometer (Medishield) in the expiratory circuit, thereby maintaining the levels of pCO_2 between 3.8-4.5 kPa. During the monitoring of SV, by impedance cardiography, however, a constant ventilation was provided in all the subjects. At the end of surgery the muscular paralysis was reversed with atropine 1.0 mg and neostigmine 2.5 mg, and fentanyl-induced respiratory depression by naloxone 0.2 mg i.v. Postoperatively the patients were allowed to inhale 2 l of oxygen via a nasal catheter.

The changes in the stroke volume and the heart rate were monitored continuously by Minnesota impedance cardiograph (Instrumentation of Medicine Inc. model 304 A), whereas the MAP was read from the arterial gauge, just before the insertion of acrylic cement in the acetabular cavity or the neck of femur and at 1,2,4,6,8 min intervals after its application (Table II-V, Fig. 1-4). At each interval 4 tracings of the first derivative of impedance cardiogram were taken into account and the mean value of SV calculated by applying Kubicek's equation: $\Delta V = \rho \cdot \left(\frac{L}{Z_0}\right)^2 \cdot T (dz/dt)_{\min}$ where ΔV = the ventricular stroke volume (ml), ρ = the electrical resistivity of blood at 100 kHz (ohms-cm), L = the mean distance (cm) between the two inner electrodes

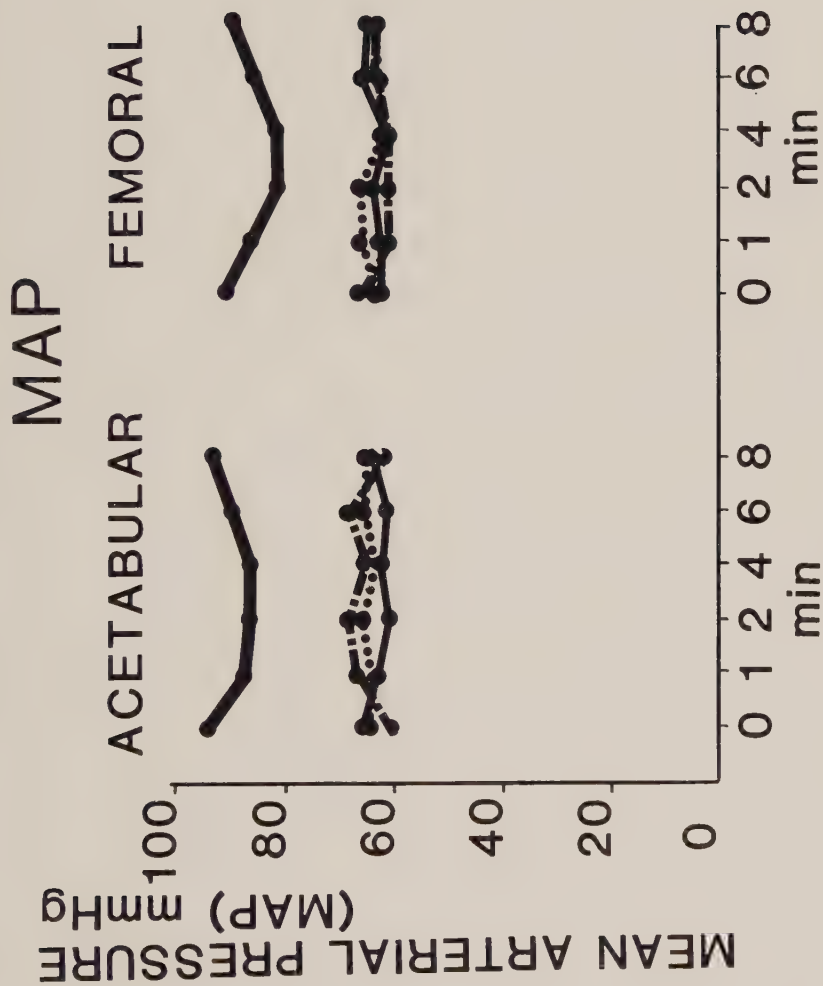


Fig. 1. Effect on the mean arterial pressure (MAP) of the acrylic monomer in acetabulum or femur before (O), and at 1,2,4,6,8 min intervals.

MAP Normotension TNP SNP GTN

(measured front and back), Z_0 = the impedance in ohms, between the two inner (potential) electrodes, $(dz/dt)_{\min}$ = ohms/sec, T = the ventricular ejection time in sec, CO = SV X HR. The corresponding value of the blood resistivity was inserted into this equation on obtaining it from the instantaneously determined value of the haematocrit, at each calculation.

RESULTS

Of 11 patients operated on under normotension after the application of acrylic cement in acetabulum, 6 showed a mean fall of 11% in MAP while 2 had an 8% reduction. In the remaining 3 cases the change was insignificant. On insertion of cement into the femur, 7 patients showed a considerable reduction in pressure (24%) while 4 individuals showed no significant change. The depression of MAP was maximal in the first 1-4 min after both insertions (Table II). During SNP and GTN-induced hypotension there were no remarkable changes observed on application of the acrylic monomer as compared with the control values (Table IV, V). Under hypotension produced by TMP, there was a slight rise of MAP in 3 cases after insertion of cement in the acetabulum. A moderate fall was seen after implantation into the femur and it was at maximum at 8-min interval in 6 patients (10%) (Table III).

In group 1, a mean reduction of 12% was noticed in the SV upon cement insertion into the acetabulum in a majority of cases while an average fall of 7% was recorded in 8 patients after femoral application. The fall in the SV was greatest in the 4-8 min after the acrylic implantation. Changes in the stroke volume during hypotension produced by SNP or GTN were insignificant, in most of the patients (Table IV, V). Under TMP hypotension there was a moderate decrease in SV in a majority of cases, both after acetabular and femoral application of the monomer (Table III).

There was no abrupt change seen in the HR upon implementation of the cement, on either of the aforementioned two sites, during deliberate hypotension. During normotension, as well, it was hard to observe anything more than a slight alteration in the heart beat. This could not be attributed to the acrylic monomer as such a minor change in rhythm is often encountered during general anaesthesia.

The acrylic cement caused little change in the CO, after its application, during hypotension induced by SNP or GTN. However, during TMP-induced hypotension there was an average reduction of 7% after acetabular insertion and a mean fall of 9% after femoral application in 8 patients. The fall was transient and the cardiac output increased towards control levels 4 min after the implantation of cement. Depression of CO at the application of acrylic material, acetabular or femoral was significant under normotension at 4-8 min period (11 and 15% fall respectively) (Table II). After acetabular insertion there was a 15% decrease in 7 cases and a 19% fall in CO in 6 patients on femoral insertion.

After the insertion of acrylic monomer the SVI and the CI, during SNP and GTN infusion, were unaltered and well maintained. A mild but transient depression of these indices was observed during TMP hypotension and was restored, in most of the cases at 6-8 min intervals. During normotension both the SVI and the CI were reduced significantly in a majority of patients on both acetabular and femoral insertions of the monomer. The fall, however, was not permanent, lasting for 5-7 minutes. Intraoperative blood-gas analysis showed a high oxygen content (pO_2 , mean 21.7, range 14.3-29.2 kPa) as compared to preoperative levels (mean 12.2, range 9.9-14.8 kPa). Reductions of pO_2 during SNP (1 case) and TMP (2 cases) were insignificant. Postoperative analysis lacked any evidence of respiratory acidosis.

Table II. Comparison of means of cardiovascular parameters before (0), and after the insertion of acrylic monomer at 1,2 4,6,8 min. intervals (AI = Acetabular insertion, FI = Femoral insertion, $P < 0.05$, Student's t test, $n = 11$) during normotension.

	AI						FI					
	0	1	2	4	6	8	0	1	2	4	6	8
	(Mean values $\pm$ S.E.M.)						(Mean values $\pm$ S.E.M.)					
MAP = Mean arterial pressure (mmHg)	94 ± 2.1	88 ± 1.9	87 ± 1.5	87 ± 1.5	90 ± 2.0	93 ± 1.8	92 ± 1.1	86 ± 1.4	82 ± 1.4	82 ± 1.4	87 ± 1.9	90 ± 1.2
SV = Stroke volume (ml)	79 ± 3.1	69 ± 1.8	69 ± 1.1	66 ± 1.1	61 ± 2.0	64 ± 1.7	66 ± 1.7	62 ± 1.4	57 ± 1.9	64 ± 1.2	64 ± 1.5	62 ± 1.9
HR = Heart rate (beats. min ⁻¹)	62 ± 1.0	68 ± 1.1	66 ± 1.2	65 ± 1.3	70 ± 1.3	68 ± 1.5	69 ± 1.3	67 ± 1.2	70 ± 1.2	64 ± 1.1	65 ± 1.2	64 ± 1.4
CO = Cardiac output (L. min ⁻¹)	4.9 ± 0.1	4.7 ± 0.1	4.6 ± 0.2	4.3 ± 0.1	4.3 ± 0.1	4.4 ± 0.2	4.6 ± 0.1	4.2 ± 0.1	4.0 ± 0.2	4.1 ± 0.3	4.1 ± 0.1	4.0 ± 0.1
SVI = Stroke volume index (ml. beat ⁻¹ . m ⁻²)	44 ± 1.0	39 ± 1.2	39 ± 1.0	37 ± 1.2	34 ± 1.5	36 ± 1.2	37 ± 1.1	35 ± 2.0	32 ± 1.4	36 ± 1.2	35 ± 1.3	36 ± 1.2
CI = Cardiac index (L. min ⁻¹ . m ⁻²)	2.7 ± 0.1	2.6 ± 0.1	2.6 ± 0.1	2.4 ± 0.2	2.4 ± 0.1	2.5 ± 0.1	2.6 ± 0.1	2.3 ± 0.1	2.2 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.09

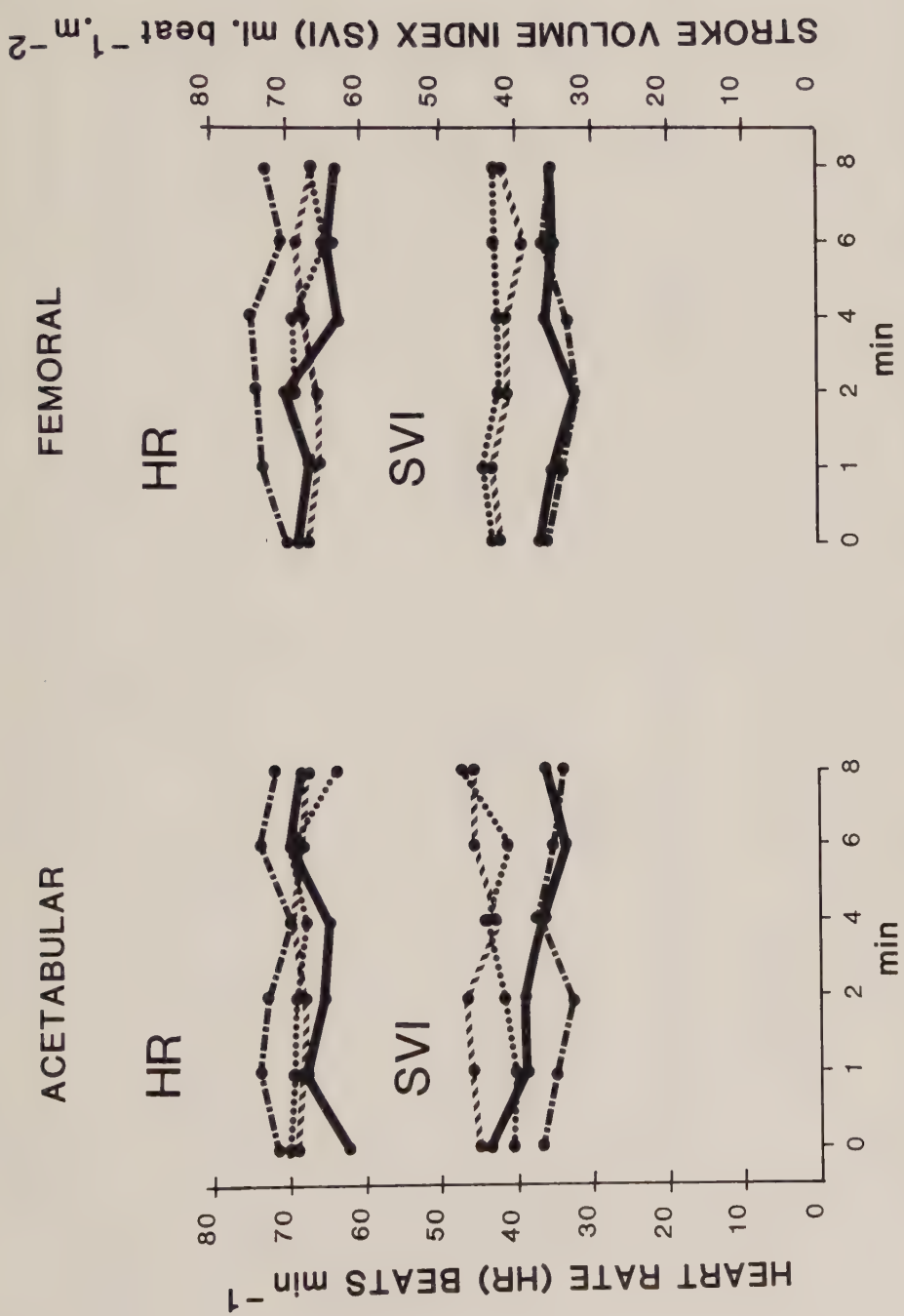


Fig. 2. Effect on the heart rate (HR) and the stroke volume index (SVI) of insertion of the acrylic monomer in acetabulum or femur before (O), and at 1,2,4,6,8 min intervals.
HR, CVI Normotension —●— TMP —●— SNP —●— GTN

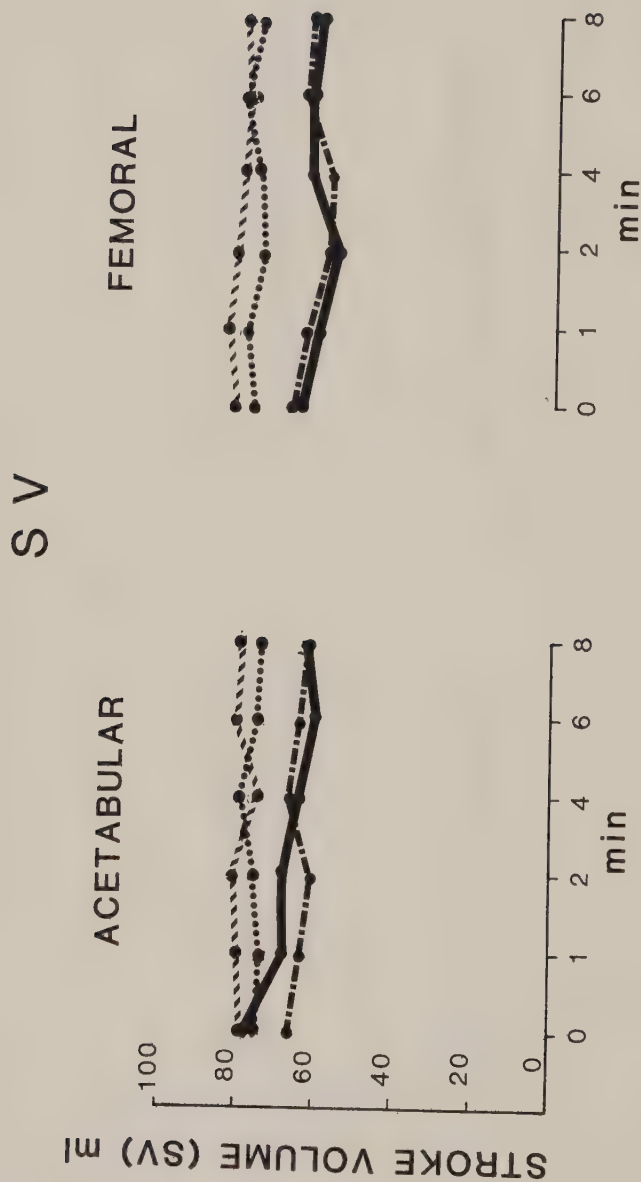


Fig. 3. Effect on the stroke volume (SV) of insertion of the acrylic monomer in acetabulum or femur before (0), and at 1, 2, 4, 6, 8 min intervals.

SV — Normotension — TMP — SNP — GTN

Table III. Comparison of means of cardiovascular parameters before (0), and after the insertion of acrylic cement at 1,2,4,6,8 min. intervals (AI = Acetabular insertion, FI = Femoral insertion, $P < 0.05$, Student's t test, $n = 9$) during TWP-induced hypotension.

	AI						FI					
	0	1	2	4	6	8	0	1	2	4	6	8
	(Mean values $\pm$ S.E.M.)						(Mean values $\pm$ S.E.M.)					
MAP = Mean arterial pressure (mmHg)	63 +1.8	66 +1.9	67 +1.4	65 +1.6	66 +1.4	62 +1.5	66 +2.0	62 +1.8	60 +1.4	61 +1.7	63 +1.5	65 +1.5
SV = Stroke volume (ml)	66 +2.1	63 +2.0	60 +2.1	67 +1.9	63 +2.1	62 +1.8	67 +1.9	63 +1.4	58 +2.0	57 +1.3	64 +1.6	63 +1.6
HR = Heart rate (beats. min ⁻¹)	72 +1.2	74 +1.1	73 +1.4	70 +1.8	74 +1.5	72 +1.5	70 +2.0	73 +1.8	74 +1.8	75 +1.9	71 +1.3	73 +1.9
CO = Cardiac output (L. min ⁻¹)	4.8 +0.2	4.7 +0.1	4.4 +0.1	4.7 +0.1	4.7 +0.3	4.5 +0.2	4.7 +0.2	4.6 +0.2	4.3 +0.1	4.4 +0.1	4.6 +0.2	4.6 +0.1
SVI = Stroke volume index (ml. beat ⁻¹ . m ⁻²)	37 +1	35 +1	33 +2	37 +2	35 +1.4	34 +1.7	37 +1.9	35 +1.8	32 +1.8	33 +1.7	36 +1.6	36 +1.9
CI = Cradiac index (L. min ⁻¹ .m ⁻²)	2.6 +0.1	2.6 +0.1	2.4 +0.2	2.5 +0.1	2.6 +0.1	2.5 +0.1	2.6 +0.1	2.5 +0.1	2.3 +0.1	2.4 +0.2	2.6 +0.1	2.6 +0.2

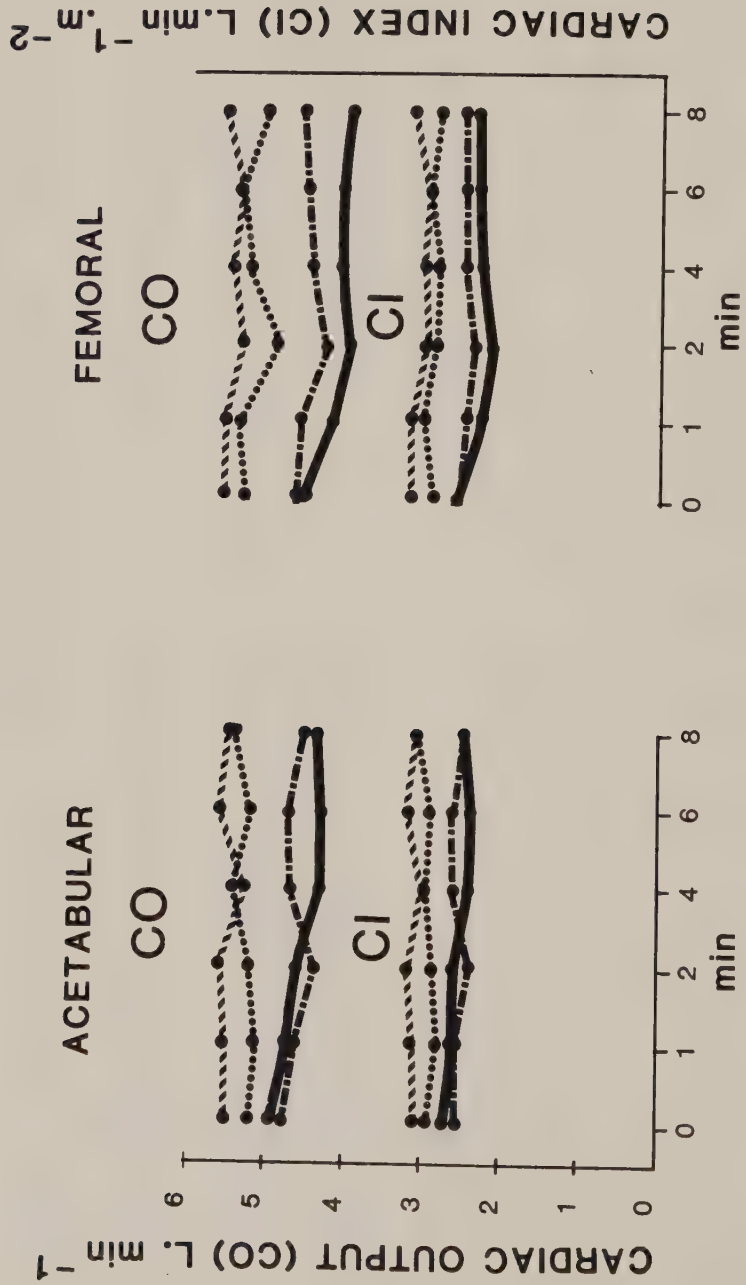


Fig. 4. Effect on cardiac output (CO) and cardiac index (CI) of insertion of the acrylic monomer in acetabulum or femur before (O), and at 1,2,4,6,8 min intervals.

CO, CI Normotension TMP SNP GTN

Table IV. Comparison of means of cardiovascular parameters before (0), and after the implantation of acrylic monomer at 1,2,4,6,8 min. intervals (AI = Acetabular insertion, FI = Femoral insertion, $P < 0.05$, Student's t test, $n = 8$) during SNP-induced hypotension.

	AI								FI									
	0	1	2	4	6	8	0	1	2	4	6	8	0	1	2	4	6	8
(Mean values $\pm$ S.E.M.)																		
MAP = Mean arterial pressure (mmHg)	65 $\pm$ 2	64 $\pm$ 1.9	62 $\pm$ 1.8	64 $\pm$ 2.2	62 $\pm$ 1.7	64 $\pm$ 2.1	63 $\pm$ 1.2	64 $\pm$ 2.3	64 $\pm$ 1.9	62 $\pm$ 2	66 $\pm$ 1.8	65 $\pm$ 1.9	63 $\pm$ 1.2	64 $\pm$ 2.3	64 $\pm$ 1.9	62 $\pm$ 2	66 $\pm$ 1.8	65 $\pm$ 1.9
SV = Stroke volume (ml)	79 $\pm$ 2.1	82 $\pm$ 3	80 $\pm$ 2.2	75 $\pm$ 2.3	81 $\pm$ 3.1	80 $\pm$ 2.3	82 $\pm$ 1.5	84 $\pm$ 2.7	81 $\pm$ 1.9	80 $\pm$ 1.9	79 $\pm$ 2.2	79 $\pm$ 3.1	82 $\pm$ 1.5	84 $\pm$ 2.7	81 $\pm$ 1.9	80 $\pm$ 1.9	79 $\pm$ 2.2	79 $\pm$ 3.1
HR = Heart rate (beats. min ⁻¹)	69 $\pm$ 2.2	68 $\pm$ 1.3	68 $\pm$ 2	70 $\pm$ 1.5	69 $\pm$ 1.9	68 $\pm$ 1.9	67 $\pm$ 1.3	66 $\pm$ 1	66 $\pm$ 1.1	68 $\pm$ 1.1	69 $\pm$ 1.2	67 $\pm$ 1.1	67 $\pm$ 1.3	66 $\pm$ 1	66 $\pm$ 1.1	68 $\pm$ 1.1	69 $\pm$ 1.2	67 $\pm$ 1.1
CO = Cardiac output(L. min ⁻¹)	5.5 $\pm$ 0.1	5.5 $\pm$ 0.2	5.6 $\pm$ 0.1	5.3 $\pm$ 0.2	5.6 $\pm$ 0.2	5.5 $\pm$ 0.3	5.5 $\pm$ 0.2	5.6 $\pm$ 0.1	5.4 $\pm$ 0.2	5.5 $\pm$ 0.1	5.4 $\pm$ 0.2	5.6 $\pm$ 0.1	5.5 $\pm$ 0.2	5.6 $\pm$ 0.1	5.4 $\pm$ 0.2	5.5 $\pm$ 0.1	5.4 $\pm$ 0.2	5.6 $\pm$ 0.1
SVI = Stroke volume index (ml. beat ⁻¹ .m ⁻²)	45 $\pm$ 3	47 $\pm$ 1	46 $\pm$ 2	46 $\pm$ 1	43 $\pm$ 1.3	46 $\pm$ 1.9	47 $\pm$ 1.2	48 $\pm$ 1.4	46 $\pm$ 2.3	46 $\pm$ 3.1	44 $\pm$ 2.2	47 $\pm$ 1.9	47 $\pm$ 1.2	48 $\pm$ 1.4	46 $\pm$ 2.3	46 $\pm$ 3.1	44 $\pm$ 2.2	47 $\pm$ 1.9
CI = Cardiac index (L. min ⁻¹ .m ⁻²)	3.1 $\pm$ 0.1	3.1 $\pm$ 0.1	3.2 $\pm$ 0.1	3.0 $\pm$ 0.2	3.2 $\pm$ 0.1	3.1 $\pm$ 0.2	3.2 $\pm$ 0.1	3.2 $\pm$ 0.2	3.0 $\pm$ 0.2	3.1 $\pm$ 0.1	3.0 $\pm$ 0.1	3.2 $\pm$ 0.2	3.2 $\pm$ 0.1	3.2 $\pm$ 0.2	3.0 $\pm$ 0.2	3.1 $\pm$ 0.1	3.0 $\pm$ 0.1	3.2 $\pm$ 0.2

Table V. Comparison of means of cardiovascular parameters before (0), and after the application of acrylic cement at 1,2,4,6,8 min. intervals (AI = Acetabular insertion, FI = Femoral insertion $P < 0.05$, Student's t test, $n = 9$) during GTN-induced hypotension.

	AI						FI					
	0	1	2	4	6	8	0	1	2	4	6	8
	(Mean values $\pm$ S.E.M.)						(Mean values $\pm$ S.E.M.)					
MAP = Mean arterial pressure (mmHg)	64 ± 2.1	64 ± 1.9	66 ± 1.8	64 ± 1.8	65 ± 1.9	66 ± 1.8	64 ± 1.2	66 ± 1.1	67 ± 1.0	62 ± 1.7	63 ± 1.8	65 ± 1.4
SV = Stroke volume (ml)	74 ± 2.0	73 ± 1.5	75 ± 1.5	79 ± 1.2	74 ± 1.2	74 ± 1.7	77 ± 1.9	79 ± 1.8	75 ± 1.8	76 ± 1.5	80 ± 1.3	76 ± 1.1
HR = Heart rate (beats. min ⁻¹)	70 ± 1.2	69 ± 1.3	69 ± 1.3	68 ± 1.2	70 ± 1.1	64 ± 1.1	68 ± 1	68 ± 1.1	69 ± 1.2	69 ± 1.1	65 ± 1.2	67 ± 1.5
CO = Cardiac output (L. min ⁻¹)	5.2 ± 0.09	5.1 ± 0.1	5.2 ± 0.2	5.4 ± 0.1	5.2 ± 0.2	5.4 ± 0.1	5.3 ± 0.1	5.4 ± 0.2	5.2 ± 0.2	5.3 ± 0.1	5.4 ± 0.1	5.1 ± 0.1
SVI = Stroke volume index (ml. beat ⁻¹ .m ⁻²)	41 ± 1.3	40 ± 1.9	42 ± 1.1	44 ± 1.1	41 ± 1.2	47 ± 1.4	43 ± 1.5	44 ± 1.4	42 ± 1.4	42 ± 1.8	43 ± 1.4	42 ± 1.4
CI = Crdialc index (L. min ⁻¹ .m ⁻²)	2.9 ± 0.1	2.8 ± 0.1	2.9 ± 0.1	3.0 ± 0.2	2.9 ± 0.1	3.0 ± 0.1	2.9 ± 0.2	3.0 ± 0.1	2.9 ± 0.1	2.9 ± 0.1	3.0 ± 0.2	2.8 ± 0.1

DISCUSSION

A marked difference in the reaction of patients in our study to the application of acrylic monomer, with regard to their blood pressure and cardiac output gives reason to believe that the monomeric cement possesses a potent vasodilator action. It was also observed that during SNP and GTN-induced hypotension, it failed to potentiate the vasodilator actions of nitroprusside or nitroglycerin at the levels of MAP (60-65 mmHg), favourable for surgical ischaemia. The mean dosage range of $1.5-2.0 \mu\text{g kg}^{-1}\text{min}^{-1}$ appeared to be sufficient to relax the vascular tree in attaining the desired levels of MAP during high-dosage fentanyl anaesthesia.

The situation is apparently modified when trimethaphan infusion is being administered and a relatively greater femoral absorption of the monomer either intensifies the weaker vasodilator action of TMP or demonstrates its own independent peripheral vasodilator effect. As to why it should occur during TMP and not with SNP or GTN, the explanation lies most probably in the elimination of an existing beta-receptor stimulation in the same manner as beta-blocking drugs do during halothane anaesthesia (Stephen, Davie and Scott, 1971). Furthermore, trimethaphan when given alone does not reduce the cardiac output and is not thought to have a direct depressant action on myocardium (Nitter-Hauge, 1977).

During normotensive anaesthesia the results of our investigation partially agreed with those of Peebles and co-workers (1972) who observed similar reductions of arterial pressure subsequent to the application of the cement in dogs. The compensatory increase in the HR and a consequential rise in the CO was, on the contrary, absent in the study reported herein. A consistent unaltered heart rhythm after the insertion of monomeric material could partly be due to an high-dosage fentanyl administration which may have suppressed the increased adrenergic response consequent upon the constant surgical stimulation.

It did not, however, block the baroreceptor response as continuous infusion of the hypotensive drugs was needed throughout the surgery, in addition to the supplementary doses of fentanyl both during induced hypotension and normotension.

The impedance plethysmography method is convenient, and being non-invasive, it is especially valuable for monitoring changes in CO repeatedly in most anaesthetised patients. The absolute values obtained by many workers during comparative evaluation of the thoracic impedance and isotope dilution methods for measurement of cardiac output, demonstrate frequent overestimations (Judy et al., 1969; Lababidi et al., 1971; Rasmussen, Sørensen and Kann, 1975). Although less precise in absolute terms than invasive techniques, the results are reproducible and accurate (Baker et al., 1971; Hill and Lowe, 1973; Kubicek et al., 1974; Hill and Thompson, 1975; Casthely, Ramanathan and Chalon, 1980). The general opinion is that in order to improve accuracy the knowledge of the blood resistivity corresponding to the instantaneously determined haematocrit value, is essential for each calculation of stroke volume. The changes in magnitude are thereby, thought to be comparable with those obtained by the dye-dilution techniques.

From the data collected during this study we found that there was a predominant but transient depression of the MAP and CO during normotension or TMP-induced hypotension, on the insertion of the acrylic cement. The changes in these parameters were insignificant during SNP or GTN-induced hypotension. It seems appropriate to assume that a short period of time is often needed by the human circulation to adjust to the monomer-induced changes in haemodynamics during the general anaesthesia as well as after the ganglion blockade.

We would, therefore, suggest that as a result of this investigation, sodium nitroprusside or nitroglycerin are preferable to trimethaphan in producing deliberate hypotension during hip arthroplasty.

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